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DYNAMICS OF THE ACTION OF PENICILLIN IN EXPERIMENTAL ANIMALS

Observations on Mice

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SAN FRANCISCO

IN THE last few years penicillin has established itself as a drug of great therapeutic value, possessing in a high degree the characteristics of an ideal antiseptic: exceedingly low toxicity and high bactericidal and bacteriostatic efficiency. The great demand for this drug in wartime and the early difficulties of large scale production made it imperative to use the minimal effective dosage. Arbitrary dosage schedules were selected by clinical trial and notable successes were achieved, but there is little evidence to show that the dosage used was optimal or even the most economical.

Early systematic studies [1] demonstrated that penicillin is rapidly excreted in the urine after parenteral administration. It has been generally accepted in the past that a sustained blood level of the drug is essential and, therefore, that it must be administered either continuously or at frequent intervals or that special methods must be used to retard its absorption or excretion.[2] There is, however, no good evidence that such maintenance of measurable blood levels is always essential, nor has the duration after infection of the action of the drug on the parasite population been determined.

The experimental work presented in this paper was designed to answer the following questions: 1. Can penicillin action be demonstrated in vivo only as long as measurable blood levels of the drug are present? 2. What is the effect on the therapeutic results of the length of the intervals between injections? 3. What is the optimum relationship between magnitude of dose and interval of time between injections?

From the Department of Medicine, Stanford University School of Medicine.

1. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**:425, 1943.

2. (*a*) Romansky, M. J., and Rittman, G. E.: Method of Prolonging Action of Penicillin, Science **100**:198, 1944. (*b*) Rammelkamp, C. H., and Bradley, S. E.: Excretion of Penicillin in Man, Proc. Soc. Exper. Biol. & Med. **53**:30, 1943. (*c*) Beyer, K. H.; Woodward, R.; Peters, L.; Verwey, W. F., and Mattis, P. A.: Prolongation of Penicillin Retention in Body by Means of Para-aminohippuric Acid, Science **100**:107, 1944.

The clarification of these points seems worth while, for, in spite of the rapid advances being made at present in the development of penicillin for oral use, it is felt that parenteral administration will be utilized for some time in the treatment of severe infections. It is possible that on the basis of experimental work dosage schedules for penicillin treatment might be devised which could combine greater effectiveness than in the past with increased comfort for the sick. If, for example, larger doses at six hour intervals could be demonstrated to be as effective as smaller ones given three hours apart, such a development might materially benefit the patient.

In the experimental approach to this question it was first necessary to establish a laboratory "model" lending itself to the study of some of the factors involved. After preliminary standardization of a streptococcic infection in mice and its treatment with penicillin, the problem was attacked by two methods:

1. Observation of survival rates in animals treated with different amounts of penicillin with varying intervals of time between injections.

2. Study of the effects of parenterally administered penicillin on the bacterial population in the heavily infected host by means of cultures of tail blood, cultures of peritoneal fluid and bacteriologic autopsies.

METHODS

1. *Infection.*—A virulent beta hemolytic streptococcus, strain G22R (Lancefield group A, type 3), isolated from a patient with sore throat, was used as the infecting agent throughout all experiments. The average lethal dose was approximately 500 organisms injected intraperitoneally into white mice. The strain was maintained in the frozen state at —70 C. without change in virulence for nine months. The standard inoculum was prepared by subculturing 0.5 cc. of the thawed stock culture in 5 per cent horse blood broth for eight to ten hours at 37 C. Five-tenths cubic centimeter of this culture was transferred to ordinary meat extract broth, incubated for ten to twelve hours at 37 C. and then serially diluted in cooled broth blanks. The standard inoculum consisted of 0.5 cc. of a 1:1,000 dilution containing approximately 15,000 to 150,000 organisms injected intraperitoneally. Strain G22R proved to be highly sensitive to penicillin. Broth cultures of the streptococcus were regularly completely inhibited by 0.001 unit of penicillin per cubic centimeter.

2. *Experimental Animals.*—A uniform strain of white Swiss mice was used, the average weight being 15 to 22 Gm. Ninety-eight per cent of all untreated animals infected with the standard inoculum died within twenty-four hours.

3. *Penicillin.*—The sodium salt of penicillin was made up in solutions of the desired strength with sterile isotonic solution of sodium chloride. Blood levels of penicillin were determined by the method of Wolohan and Cutting [3] on whole citrated blood obtained by cardiac puncture of mice lightly anesthetized with ether.

3. Wolohan, M., and Cutting, W.: A Modified Method for Measurements of Penicillin Blood Levels, J. Lab. & Clin. Med. **30**:161, 1945.

4. *Treatment.*—The first injection of penicillin was always given four hours after infection, and subsequent treatments were given at intervals of from four to sixteen hours. An appropriate amount of the drug was contained in 0.2 cc., which was injected intraperitoneally or into the thigh muscle. After treatment, the mice were observed for seven days and deaths were noted. The cause of death was checked for about half the mice by culturing the heart blood.

5. *Cultures of Tail Blood.*—The tail was cleaned with dilute saponated solution of cresol and alcohol in the usual way; then it was cut with sterile scissors, and 2 drops of blood were streaked on a segment of a blood agar plate.

6. *Cultures of Peritoneal Fluid.*—At various intervals 1 cc. of sterile isotonic solution of sodium chloride was injected intraperitoneally and the abdomen massaged for one minute. Fluid was then withdrawn by capillary pipet, and 2 uniform drops were cultured on blood agar plates.

7. *Bacteriologic Autopsies.*—The method followed was essentially that described previously.[4] At various intervals after infection and treatment, small groups of mice were anesthetized with ether and autopsies were performed with sterile instruments under strictest aseptic precautions. Cultures were taken in the following sequence: (*a*) 2 drops of tail blood, obtained as indicated; (*b*) scrapings from the peritoneum and a loopful of peritoneal fluid, (*c*) lymph node juice (the para-aortic celiac lymph nodes were dissected out and squeezed and the juice plated); (*d*) uniformly cut surfaces of spleen and liver smeared over standard segments of blood agar plates, and (*e*) a large drop of heart blood. Occasionally bone marrow from the femur was also cultured. All cultures were made on 10 per cent horse blood agar plates, without penicillin inactivator, and incubated for twenty-four hours at 37 C. After incubation the plates were either sterile (occasional contaminants were present on the segments that had been touched with the cut tail) or showed the characteristic colonies of the streptococcus surrounded by a marked zone of hemolysis. Frequently one or more segments was completely hemolyzed, with confluent growth of the organisms. Results were recorded in the following terms: *0* = blood plate segment sterile; *1-35* = actual number of colonies of hemolytic streptococci counted per segment; *c* = more than 35 colonies per segment or confluent growth. One cannot lay claim to absolute accuracy for this method, but its results have comparable value. Arguments for its validity have been presented elsewhere.[4]

RESULTS

1. *Blood Levels of Penicillin in Mice.*—After intramuscular or intraperitoneal injection of 30 units of penicillin into 20 Gm. mice absorption and excretion were very rapid, the curve of blood levels being similar to that observed for human beings.[1] Chart 1 indicates that one hour after injection 0.03 unit per cubic centimeter of whole blood was present. Twenty minutes later only traces of penicillin and fifty minutes later no bacteriostatic activity of the blood at all could be detected. Similar results were obtained with doses up to 150 units. It seems, therefore, that most of the injected penicillin was absorbed and excreted within eighty minutes after injection. Attempts to determine the actual amounts

4. Jawetz, E., and Meyer, K. F.: Behavior of Virulent and Avirulent P. Pestis in Normal and Immune Experimental Animals, J. Infect. Dis. **74**:1, 1944.

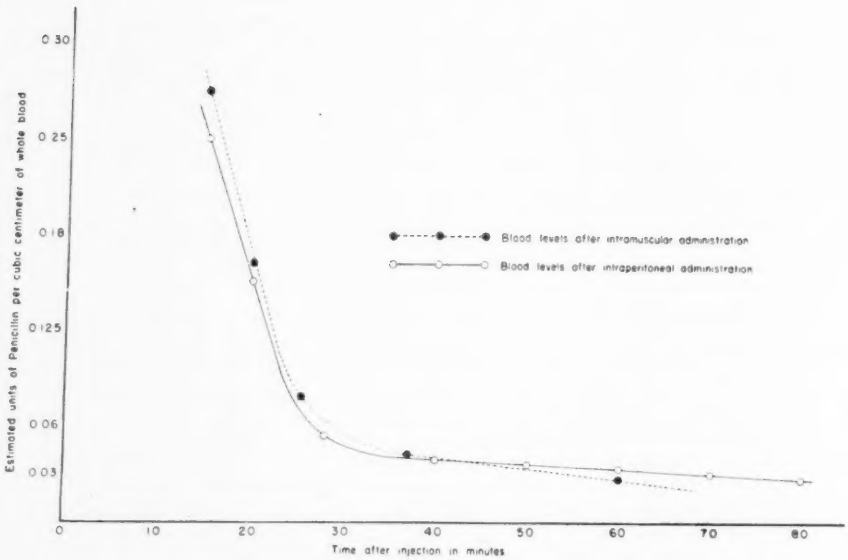

Chart 1.—Blood levels of penicillin in mice after intramuscular or intraperitoneal administration of 30 units.

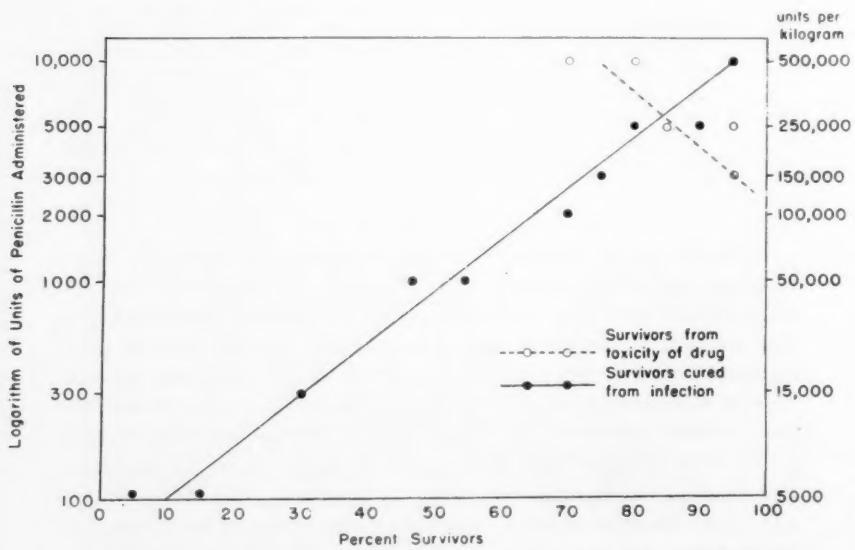

Chart 2.—Effect of large single doses of penicillin given intramuscularly on the rate of survival of mice from a severe streptococcic infection. Ninety-eight per cent of all controls die in eighteen hours.

excreted failed because of the great technical difficulty of quantitative collection of urine from small animals.

2. Results of Penicillin Treatment Determined by Survival Rates.—A. Effects of a Single Dose: As shown in chart 2, single doses of less than 50,000 units per kilogram of body weight given intramuscularly did not save more than 50 per cent of the animals. There appeared to be a linear increase in the survival rate with a logarithmic increase in the dose. Ninety-five per cent of the experimental animals that had survived the toxic impact of the injection were cured by a dose of 500,000 units per kilogram. Twenty to 30 per cent of the mice died from acute toxicity within ten to thirty minutes after injection of this amount of penicillin. Within five to eight minutes after treatment such animals had labored, gasping respiration, rapidly became prostrated and somnolent, with sunken flanks and great muscular weakness, and soon died in respiratory failure. No deaths from toxicity were observed with doses below 100,000 units per kilogram. It was uncertain whether the toxic effects were to be attributed to the active penicillin itself or to an impurity in the preparation.

B. Effects of Three Equal Intramuscular Injections Given Four Hours Apart: Again, a fair correlation was observed between the logarithm of the dose of penicillin and the survival rate, as shown in chart 3. In marked contrast to the experience with single doses, however, the amount of penicillin necessary was much smaller. Optimal results, or survival of more than 85 per cent of the animals, were obtained with 5,000 units per kilogram, and no toxicity was observed.

C. Effect of Three Injections of 30 Units of Penicillin Each, Given Intraperitoneally or Intramuscularly, from Four to Sixteen Hours Apart: Representative results of a series of experiments are presented in table 1. Good results were obtained even when treatments were spaced

TABLE 1.—*Effect of Treatment with Three Equal Doses of Penicillin (30 Units Each) Administered at Various Intervals*

				Percentage of Survivors						
				Intraperitoneal Treatment:			Intramuscular Treatment:			
Experiment No.	No. of Mice per Group	Average Weight of Mice, Gm.	Dose per Kilogram, Units	Interval Between Injections			Interval Between Injections			Untreated Controls
				4 Hr.	8-10 Hr.	16 Hr.	4 Hr.	8-10 Hr.	16 Hr.	
5	20	22	4,100	80	40	30	65	55	20	0
6	20	16	5,600	85	85	60	90	80	70	5
7	20	15	6,000	90	80	55	90	95	60	0

eight to ten hours apart, provided the total dose was kept above approximately 5,000 units per kilogram. The rate of cure below this level was definitely unsatisfactory with intervals of more than four hours between

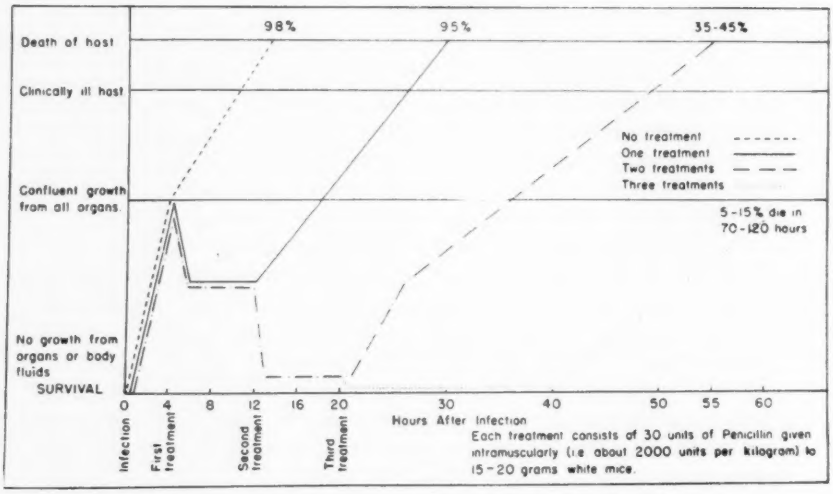

Chart 3.—Effect of three equal doses of penicillin administered intramuscularly at intervals of four hours on the rate of survival of mice from a severe streptococcic infection. Ninety-eight per cent of all controls die in eighteen hours. The logarithm of the total amount of penicillin administered is given on the ordinate.

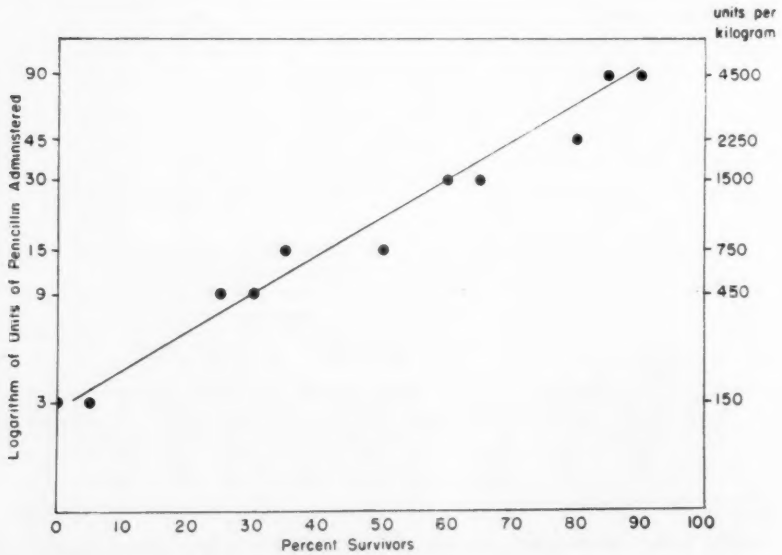

Chart 4.—Effect of penicillin on a severe streptococcic infection in mice. The chart is a composite schematic representation of the action of intramuscularly administered penicillin on the bacterial population in the host.

treatments. In addition to the saving of life, the survival time of animals dying in spite of treatment was greatly increased. Most controls died within eighteen to twenty hours after infection, whereas animals dying after treatment lived for an average of ninety hours.

D. Results of Postponing the Beginning of Treatment Until Symptoms Appear: As will be pointed out subsequently, the infecting organisms were disseminated very rapidly throughout the body of the host and were usually present in all organs three to four hours after inoculation. At that time no signs of infection were present and the mice appeared to be perfectly well. About eight or nine hours after infection the earliest lassitude and roughening of the fur was noticed and the peripheral blood contained many streptococci. Treatment started at this time prolonged life for forty-eight hours but never cured more than 10 per cent of the group, even when three doses of 100 units were given four hours apart. This large amount of penicillin kept the peripheral blood free from organisms until shortly before death but apparently was unable to restore the activity of the animal's impaired defense mechanism.

TABLE 2.—*Comparison of the Effects of One, Two and Three Doses of 30 Units of Penicillin Given Intramuscularly 8 Hours Apart*

Experiment No.	No. of Mice per Group	Average Weight of Mice, Gm.	Percentage of Survivors			
			No Injection	One Injection	Two Injections	Three Injections
1	20	17	0	5	60	85
2	20	19	0	10	55	90
3	16	16	6	0	62.5	87.5

E. Relative Effect of One, Two and Three Injections of 30 Units of Penicillin Each: After it was observed that three injections of penicillin commonly cured all, and one injection none, of the animals, it became imperative to determine just where in the treatment the maximal effect was achieved. Suitable experiments, as shown in table 2, indicate that apparently the second injection most significantly raised the rate of cure while the third dose seemed to tip the balance for only a small number of the animals. These tests purposely were carried out with intervals of eight hours between treatments in order to demonstrate more precisely minor differences which might be hidden by overlapping effects of doses given only a short time apart.

3. *Cultures of Tail Blood.*—Cultures of the tail blood of untreated mice were always positive for streptococci six to eight hours after inoculation. Injection of penicillin at a time when many streptococci were were present in the peripheral blood usually cleared the blood stream but rarely cured the mice. A single dose of 30 units of penicillin usually kept cultures of tail blood sterile for twenty to thirty hours and until four to

eight hours before death. This apparent sterilization of the blood stream had no prognostic significance and could not be used as a guide to therapy. Probably the penicillin enabled the filtering organs (spleen, liver and bone marrow) to retain streptococci efficiently until overwhelming toxemia set in.

4. *Cultures of Peritoneal Fluid.*—Two objections militate against the use of this method. Repeated punctures of the abdominal cavity were certain to produce serious injury and thereby impair the animal's general resistance. In addition, the local trauma produces inflammation, outpouring of fibrin and fixation of bacteria. Thus one might expect to find apparent sterility of the peritoneal fluid due to the firm fixation of organisms in the fibrin meshes on the serous surfaces. Keeping these pitfalls in mind, one may summarize the essential results obtained by this method as presented in table 3 as follows: There was no striking disappearance

TABLE 3.—*Cultures of Peritoneal Washings*

	No Injection: Mouse No.				One Injection: Mouse No.				Two Injections: Mouse No.				Three Injections: Mouse No.			
Time, Hr.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
0	Infected				Infected				Infected				Infected			
2	c	c	c	c	c	c	c	8	c	5	c	c	20	c	10	c
4	c	20	c	c	Treated				Treated				Treated			
5	c	c	30	c	c	35	c	c	c	20	35	c	12	c	c	14
7	c	c	c	c	c	20	10	c	—	—	—	—	4	30	c	c
9	c	c	c	c	c	15	c	c	26	30	c	8	—	—	—	—
11	25	c	c	35	—	—	—	—	c	13	c	20	30	14	c	29
12	—	—	—	—	—	—	—	—	Treated				Treated			
13	c	c	c	c	c	20	35	35	c	0	30	0	20	2	c	0
15	c	c	+	c	c	11	3	25	30	0	c	0	0	0	c	0
19	+	c	—	+	c	c	0	c	c	0	35	0	0	0	0	10
20	—	—	—	—	—	—	—	—	—	—	—	—	Treated			
21	—	c	—	—	c	c	c	c	30	0	20	0	0	0	0	0
25	—	+	—	—	+	c	+	c	c	0	22	0	0	0	10	0
30	—	—	—	—	c	+	—	c	+	8	c	c	0	0	c	0
40	—	—	—	—	—	—	—	+	—	0	c	+	0	0	c	0
50	—	—	—	—	—	—	—	—	—	0	+	—	0	0	+	0
60	—	—	—	—	—	—	—	—	—	S	—	—	S	S	—	S

Meaning of symbols: Infected = standard inoculum intraperitoneally; treated = 30 units of penicillin intramuscularly; c = confluent growth, or more than 35 colonies with hemolysis on plate; 1-35 = number of colonies with hemolysis counted on plate; — = not tested; + = animal died; S = animal survived.

of streptococci after the first intramuscular dose of 30 units of penicillin but only a slight reduction in number lasting for eight to twelve hours. The second injection, four to eight hours after the first, produced a significant drop in bacterial count which persisted for ten to fifteen hours. Gradually the streptococcic population returned in most animals, reaching its former level about twenty hours after the second injection. The third dose of the drug usually brought about the complete and permanent disappearance of bacteria from the peritoneum.

5. *Bacteriologic Autopsies.*—From previous experience [4] it appeared likely that the systematic survey of the bacterial population in the body of the host would give the most balanced and most reliable information

about the influence of penicillin on the course of the infection. Consequently, a number of experiments were performed with this technic. Tables 4 and 5 are sample protocols representative of the results obtained. A summary of the more important observations follows.

A. Normal Course of the Infection: Within three to four hours after inoculation, there was confluent growth of the cultures from peritoneum, celiac lymph nodes (draining the peritoneum), spleen and liver and usually from heart blood. Only occasional organisms could be recovered from the tail blood, and the animals appeared clinically well. Six to eight hours after infection the first signs of illness were noted and increasing numbers of bacteria were present in the tail blood; the celiac nodes were somewhat enlarged, and the peritoneal exudate was viscid. Nine to eleven hours after inoculation the mice were seriously ill and listless, the celiac nodes were more enlarged and the spleen was slightly enlarged. From then on the animals deteriorated rapidly and died in twelve to twenty hours. Throughout the illness all internal organs and the bone marrow yielded innumerable streptococci on culture.

B. Infection Modified by Intraperitoneal Penicillin Treatment: Within two hours after injection intraperitoneally of 30 units of penicillin there was a pronounced reduction of the bacterial growth from all organs. Growth on cultures of the organs remained at a low level for six to nine hours, then gradually increased until death. The tail blood remained sterile for eight to twelve hours after treatment and became positive for streptococci only as signs of illness appeared.

A second injection of the drug, given four to eight hours after the first, further reduced the number of streptococci, so that some animals appeared "sterilized" while others showed bacteria only in the spleen or liver. This marked depression of the bacterial population lasted for six to eighteen hours; then proliferation again started throughout the body. A third injection given during this period of depression usually cleared the host permanently.

C. Intramuscular Treatment: The effects of the first intramuscular dose of 30 units were usually much less dramatic than those with intraperitoneal treatment. Only slightly fewer bacteria could be recovered for six to nine hours than before treatment. The second dose during this period produced a sudden clearing of the body, lasting for eight to twelve hours. Some animals went on to permanent recovery, but most showed a return of the bacterial population. If a third injection was given during this depression, there was a rather gradual disappearance of streptococci over a period of hours. Sometimes a few organisms could be isolated from the spleen or liver as late as twelve to eighteen hours after the third dose; yet most of the control animals survived. This probably indicated that penicillin reduced the number of bacteria considerably and kept them

TABLE 4.—*Bacteriologic Autopsies: Effect of Intraperitoneal Injections of Penicillin*

Time, Hr.	No Treatment (Control)						One Treatment						Two Treatments						Three Treatments					
	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood
0			Infected						Infected						Infected						Infected			
2	c	c	25	c	8	0																		
	20	c	c	10	0	0																		
	c	c	c	c	20	1																		
4	c	c	c	c	c	5			Treated						Treated						Treated			
	c	c	c	c	c	1																		
	25	15	c	c	7	0																		
5	c	c	c	c	c	0	c	c	c	c	12	0	c	c	20	16	0	0	8	30	12	c	17	2
	c	c	c	c	c	4	5	c	c	c	9	1	c	c	c	c	c	8	c	c	c	c	c	0
	c	c	c	c	6	0	c	c	c	c	23	0	6	30	15	c	30	0	c	c	c	c	14	0
7	c	c	c	c	c	25	7	0	25	c	0	0	0	0	1	0	0	0	1	0	5	25	0	0
	30	c	c	c	21	0	0	0	20	5	0	0	7	24	c	19	1	0	0	0	0	0	0	0
	c	c	c	c	c	12	20	20	25	c	0	0	0	0	5	17	0	0	0	1	10	23	0	0
8	—	—	—	—	—	—	—	—	—	—	—	—			Treated						Treated			
9	c	c	c	c	c	c	1	8	15	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	c	c	c	c	c	35	0	0	1	1	0	0	0	0	0	1	0	0	0	0	0	3	0	0
	c	c	c	c	c	0	0	25	30	4	0	0	20	10	30	21	4	0	1	1	2	0	0	0
11	c	c	c	c	c	c	2	2	6	15	15	0	0	0	1	0	0	0	10	0	2	5	5	0
	c	c	c.	c	27	4	15	0	8	19	20	0	0	0	0	0	0	0	0	9	11	c	0	0
	c	c	c	c	c	c	20	30	10	28	11	0	0	0	1	4	1	0	1	5	25	3	0	0
12	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			Treated			
13	c	c	c	c	c	30	c	c	c	c	c	0	0	0	5	22	0	0	0	0	0	0	0	0
	c	c	c	c	c	c	16	17	c	21	c	1	7	23	9	35	2	0	0	0	0	0	0	0
	c	c	c	c	c	11	4	c	15	c	25	0	0	8	0	10	0	0	0	0	3	13	0	0
15	c	c	c	c	c	c	20	30	c	c	18	0	15	35	c	26	4	0	0	0	0	0	0	0
			Dead				c	c	30	20	1	0	0	0	8	c	3	0	0	0	0	0	0	0
			Dead				25	10	c	c	30	1	0	0	0	3	0	0	0	0	0	0	0	0
24	—	—	—	—	—	—	c	c	c	c	c	8	10	29	c	c	21	2	0	0	0	0	0	0
							9	c	c	c	c	20	c	c	c	c	c	c	0	0	0	0	0	0
							c	c	c	c	c	c	c	c	c	c	c	17	0	0	0	0	0	0

Meaning of symbols: see table 3.
Treatment: 30 units penicillin intraperitoneally at four hour intervals.

TABLE 5.—*Bacteriologic Autopsies: Effects of Intramuscular Injections of Penicillin*

Time, Hr.	No Treatment (Control)						One Treatment						Two Treatments						Three Treatments					
	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood	Peritoneum	Celiac Lymph Nodes	Spleen	Liver	Heart Blood	Tail Blood
0			Infected						Infected						Infected						Infected			
4	c	c	c	c	c	20			Treated						Treated						Treated			
	c	c	c	c	c	c																		
	c	c	c	c	c	25																		
5	c	c	c	c	c	3	c	15	25	c	20	1	24	4	25	30	2	1	35	20	20	10	3	0
	c	c	c	c	c	c	12	30	c	c	18	1	20	35	c	c	c	0	4	2	21	29	16	3
	20	35	c	c	c	0	27	c	c	c	9	0	c	c	c	c	c	3	10	10	35	c	6	0
8	c	c	c	c	c	25	3	10	c	15	3	0	26	4	20	25	15	10	c	c	c	c	15	2
	c	c	c	c	c	c	c	20	15	8	1	0	7	11	c	c	14	0	0	5	3	0	0	0
	c	c	c	c	c	c	10	3	8	4	3	1	c	c	c	c	c	0	c	20	c	15	5	1
11	30	25	c	c	20	2	8	3	7	c	20	1	21	17	30	c	15	3	c	c	c	c	20	3
	c	c	c	c	c	c	20	c	c	c	30	10	c	8	20	35	c	0	10	21	26	c	c	0
	c	c	c	c	c	9	c	c	32	c	c	5	7	4	20	5	1	0	2	9	12	4	1	0
12	—	—	—	—	—	—	—	—	—	—	—	—			Treated						Treated			
13	c	c	c	c	c	c	12	c	c	..	20	0	2	8	20	14	3	0	5	c	30	27	4	0
	c	c	c	c	c	c	10	12	21	28	14	2	0	1	2	1	0	0	0	0	1	1	0	0
	c	c	c	c	c	16	19	35	c	20	1	0	0	0	2	25	1	0	0	0	0	0	0	0
15	c	c	c	c	c	c	8	24	c	c	30	2	0	0	0	0	0	0	4	20	4	8	0	0
	c	c	c	c	c	c	c	c	c	c	c	1	15	11	21	13	4	0	8	c	c	c	8	16
			Dead				c	c	c	c	c	0	9	22	15	31	10	0	0	0	0	4	7	0
19			Dead				c	c	c	c	c	9	0	0	0	0	0	0	0	10	14	7	0	0
			Dead				c	c	c	c	c	c	20	26	31	c	6	1	7	3	15	6	10	0
			Dead				c	c	c	c	c	c	10	4	c	c	30	0	0	2	21	16	4	0
20			—						—				—								Treated			
21			—						Dead				20	2	2	1	3	0	8	19	34	16	5	1
									Dead				c	c	c	c	c	20	0	0	0	0	0	0
									Dead				3	7	20	6	0	0	0	0	0	5	0	0
25			—						Dead				c	c	c	c	c	13	1	6	4	3	1	0
									—				c	c	c	c	c	c	0	0	0	0	0	0
													23	6	19	c	31	12	0	0	0	0	0	0
40			—						—				5	c	20	20	0	0	0	1	0	1	0	0
													c	c	c	c	c	8	0	0	0	0	0	0
															Dead				0	0	0	0	0	0

Meaning of symbols: see table 3.
Treatment: 30 units penicillin intramuscularly at eight hour intervals.

at a low level for some time, permitting the normal body defense mechanisms to dispose of the few stragglers.

The question was also investigated as to whether the mice acquired some degree of immunity during their brief illness. If so, the final clearance of the body might be due to immune reactions rather than to normal body defenses. To clarify this question, groups of normal unused mice were compared with groups that had been cured twice of their infection by treatment with penicillin. As seen in table 6, no significant increase in

TABLE 6.—*Comparison of the Resistance to Streptococcic Infection of Normal and of Twice Exposed Mice*

Experiment Number	Animals per Group	Percentage of Survivors	
		Normal Mice	Twice Exposed Mice
1	50	2	8
2	40	0	2.5

resistance could be found in the twice exposed mice. Admittedly, however, this test may have been too stringent to detect minor differences in acquired immunity.

COMMENT

The results obtained in this study indicate quite definitely that the success of parenteral penicillin therapy for mice depends on both the quantity of penicillin administered and the interval between injections. Small amounts had to be given very frequently in order to save a significant portion of infected animals, but if large doses were used injections could safely be spaced eight to ten hours apart and excellent results obtained. A single injection sufficed to cure the majority of animals when very large doses of penicillin were used, whereas with small amounts frequently repeated administration was necessary.

It could be shown definitely that the effects of penicillin on the bacterial population in the host lasted much longer than the measurable blood levels. The latter persisted for only about one hour after the injection of penicillin, while the depression of the bacterial population continued for six to eight hours or longer. The final clearance of streptococci from the body, occurring often many hours after the last injection of penicillin, probably may be ascribed to normal body defense mechanisms. No significant immunity could be demonstrated in surviving experimental animals cured by the drug. The prolonged inhibition of bacterial proliferation in the absence of significant blood levels of penicillin must be attributed to one or more of the following mechanisms:

A. Presumably most of the penicillin circulating in the blood stream during the first hour after administration is excreted through the kidneys. It is possible, however, that very minute quantities remain in the tissues

and are sufficiently bacteriostatic to prevent free multiplication of bacteria. The cures obtained with very large single doses of penicillin might be due to failure of rapid tubular excretion with longer maintenance of significant concentrations of penicillin in the tissues.

B. The first impact of high penicillin levels shortly after administration may either kill a large proportion of the original streptococcus population or else so damage their enzyme systems that multiplication is severely inhibited for several hours.

C. The early high penicillin levels may injure the micro-organisms in such a way as to make them much more accessible to the normal body defenses, especially phagocytosis and filtration. Thus the host is able to cope effectively with relatively large numbers of bacteria for several hours.

Quite certainly the filtration mechanism of liver, spleen and bone marrow is much more efficient for many hours after the injection of penicillin. This probably explains the frequently negative results of culture of peripheral blood in spite of abundant growth of streptococci from all internal organs. "Sterilization of the blood stream," measured by culture of peripheral blood after penicillin treatments, seems to have no prognostic value whatever and is merely the result of improved retention of bacteria by the blood-filtering organs.

It was felt that it was possible, by combining the significant results of this study, to draw up a schematic representation of penicillin action as observed in mice. Chart 4 demonstrates that untreated animals harbor many streptococci in all organs four hours after infection, become ill six to eight hours later and succumb to the infection to within twelve to twenty hours. One intramuscular injection of penicillin four hours after inoculation produces a moderate fall of the bacterial population, which is maintained at an intermediate level for six to eight hours but then rapidly increases, so that 95 per cent of the animals are dead in thirty hours. Thus, up to a dose of 5,000 units per kilogram the first injection never cures. It fails to reduce the number of bacteria to levels susceptible to the normal clearing mechanism of the body. With larger doses, as shown in chart 2, this may occasionally occur, but 50,000 units per kilogram is required to cure 50 per cent of the mice with a single injection. Ten times that dose kills 20 to 30 per cent of the animals by immediate toxicity but cures all others. If one assumes that the toxicity is due to contaminating materials rather than to the active principle of the drug, it may conceivably be possible safely to treat and cure an acute streptococcic infection with a single large dose given intramuscularly (e.g., about 40,000,000 units for a man of 70 Kg.).

If a second dose of penicillin is administered at any time during the "depressed level" following the first injection, there is a rapid, marked drop of bacterial counts to a lower plane. Many animals are apparently

able to destroy the remaining organisms, for over 50 per cent remain cured after the second injection. The rest die in an average of fifty-five hours. The injection of a third dose during the second depression assists the body defenses in the control of the residual organisms and permits the cure of the majority of animals. Occasionally no bacteria can be recovered for twenty hours after the third dose of penicillin, but later they reappear and kill 5 to 15 per cent of the mice.

The importance of the size of the dose of penicillin in the treatment of experimental animals has been established. It was clearly shown that the rate of survival of treated animals was directly proportional to the amount of penicillin administered per dose. When larger doses were given, fewer injections were necessary and longer intervals between injections were permissible with satisfactory results. There was no "upper limit" of the useful dose of penicillin except that imposed by toxicity phenomena. With very large doses, exceeding 50,000 units per kilogram, more than half of the animals—that would all have died if untreated—could be saved by a single injection of the drug, without resort to "absorption-slowing" devices. With 100,000 to 150,000 units per kilogram, just below the minimal toxic dose, about 75 to 85 per cent of the animals are cured by a single injection, while 98 to 100 per cent of the controls die.

These figures seem sufficiently impressive to warrant serious consideration in clinical medicine. While, obviously, no results obtained on mice can be applied to human beings, it may be of considerable interest to speculate about the possible clinical implications of this experimental work. If penicillin action lasts as long in persons as it does in mice, it may be quite permissible to give injections to patients six to eight hours apart. At the same time the daily dose would have to be kept above 5,000 units per kilogram, or approximately five times the minimal inhibiting dose in vitro, since it was at this level only that the long intervals were as satisfactory as shorter ones. It would seem advisable to give larger amounts of the drug to all patients now that supplies are no longer restricted and the cost is not prohibitive. The striking cures obtained with very large single doses in mice certainly suggest their trial in human disease. There appear to be no contraindications to very large doses that do not exceed the toxic level of the preparation used. The sensitivity phenomena are probably not influenced by dosage and are rarely significant. Clinical trial of doses between 20,000 and 100,000 units per kilogram per day seems indicated, not only for chronic infections with organisms partly resistant to penicillin, such as subacute bacterial endocarditis, but also for malignant acute infections. The safety factor and ease of cure would thereby be greatly increased without significant dis-

advantage. Recent reports [5] indicate that the so-called "standardized" treatment schedules may be entirely inadequate for the control of infections caused by penicillin-sensitive organisms, producing bacteriologic remissions rather than cures.

The success obtained in our studies with high doses administered in short courses at intervals of six to eight hours between injections might also encourage clinical trial of relatively few large doses spaced six to eight hours apart in treatment of other bacterial infections besides gonorrhea and meningococcemia.[6] If successful, such trials may provide the basis of new, more convenient and safer methods for parenteral penicillin treatment. Experiments are in progress on experimental animals and in clinical trial to determine such optimal dosage schedules.

SUMMARY

From a study of the effects of penicillin in treatment of a severe hemolytic streptococcus infection in mice the following observations were made:

1. The success of penicillin by parenteral injection against an otherwise fatal infection of mice depended on both the quantity of penicillin administered and the interval between injections.

2. Small doses of the drug had to be given frequently (every four hours) in order to save a significant portion of infected animals, but if large doses were used injections could safely be spaced eight to ten hours apart with excellent results.

3. With very large doses a single injection sufficed to save a majority of animals.

4. By means of several bacteriologic methods it was demonstrated that the effects of penicillin on the bacterial population in the host lasted much longer than the measurable blood levels.

5. An attempt was made to elucidate the dynamics of a curative course of penicillin in mice. The possible clinical implications of the experimental results were discussed.

Dr. L. A. Rantz made suggestions and gave advice in this study, and Dr. W. C. Cutting determined the blood levels of penicillin.

5. Lapenta, R. G.; Weckstein, A. M., and Sarnoff, H.: The Inadequacy of a Standardized Dosage of Penicillin, J. A. M. A. **128**:168 (May 19) 1945.

6. Anderson, D. G.: The Treatment of Infections with Penicillin, New England J. Med. **232**:400, 1945.

VENOSPASM

Its Part in Producing the Clinical Picture of Raynaud's Disease

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ALTHOUGH many hundreds of papers have been written on Raynaud's disease, there is still no clearcut clinical concept of the mechanism involved nor an explanation for the varied pictures which are all classified under the term. The problem has been further complicated by the introduction of the term "Raynaud's phenomenon," since there is no agreement as to just what differentiates Raynaud's disease from Raynaud's phenomenon. The modern concept of Raynaud's disease which has been generally accepted is that the attack of dead whiteness in the fingers or cyanosis is due to a local fault in digital or palmar arteries, so that they constrict abnormally to cold and with nervous tension. Certain observations that we have made led us to doubt that arterial spasm can explain the entire picture of Raynaud's disease. These observations have enabled us to separate patients with the syndrome into several groups on the basis of their clinical behavior and have added clarity to our diagnosis and treatment, since we are now able to classify each patient into one or another of the groups described later, depending on which part or parts of the vascular tree must be involved to produce the clinical picture.

Our interest in the problem of Raynaud's disease and Raynaud's phenomenon was stimulated by studies on a patient who previously had been given a diagnosis of "cold allergy" and who had also received the diagnosis of Raynaud's disease. This patient, a white man aged 26, experienced swelling and cyanosis of the hands and face on exposure to cold. A basal vascular tone test [1] done by us revealed that this patient's digital arteries had a low grade of tone, since they did not constrict to cold for at least one hour, the temperature of the fingers remaining above 30 C. (86 F.) in a room in which the temperature was controlled at 20 C. (68 F.). This response is characteristic of

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1. Naide, M., and Sayen, A.: A Test for Vascular Tone in Humans and Its Application to the Study of Vascular Diseases, with Special Reference to the Etiology and Prevention of Thrombophlebitis, Am. J. M. Sc. **207**:606, 1944.

a person with relaxed arteries. At the same time it was observed that the veins became invisible with exposure to cold and the hands commenced to swell and to become cyanotic. It then occurred to us that this patient's symptoms could be explained as due to venospasm. It appeared that this might be an aberrant form of Raynaud's disease, in which abnormal constriction on exposure to cold was taking place in the veins instead of in the arteries. Subsequent measurements of the patient's venous pressure while he was exposed to cold showed the veins to be in spasm. Since nothing was apparently abnormal in the arteries, our attention became focused on the veins. While the patient was cold we attempted to measure the venous pressure in the arms. We tested the pressure in three veins in both arms, and each time it appeared that the vein was undergoing spasm. No change in pressure occurred, although, with the needle still in the vein, when a tourniquet was applied above the needle the water in the manometer rose. When the patient was warmed, the venous pressure was easily measured, and it was found to be 110 mm. of water.

Study of this patient led us to the realization that the cyanosis and swelling were similar in character to such changes that we had seen in some patients with Raynaud's disease. It seems that the signs in these patients could be explained only on the basis of venospasm as well as arterial spasm. In further observations on a group of 10 patients with Raynaud's disease and 4 patients with Raynaud's phenomenon we found that there were striking individual differences in their behavior during the attacks. In some of the patients there were signs of only arterial spasm, while in others there was clinical evidence of both arterial and venous spasm. Arterial spasm predominated over venospasm in some patients; in others the veins were the principal site of constriction.

Since the work of Lewis [2] and Landis,[3] spasm of the veins has been excluded as the principal factor in producing the clinical picture of Raynaud's disease in some patients. It is this failure to include the venous side of the vascular tree in Raynaud's disease which has created the present confusion concerning this disease, since it is impossible to explain the clinical picture in some patients by arterial spasm alone.

Some patients had only blanching of the fingers during the attack, with or without cyanosis but with visible veins on the dorsa of the

2. Lewis, T.: Experiments Relating to Peripheral Mechanism Involved in the Spasmodic Arrest of Circulation in the Fingers: A Variety of Raynaud's Disease, Heart **15**:7-101, 1929.

3. Landis, E. M., Jr.: Micro-Injection Studies of Capillary Blood Pressure in Raynaud's Disease, Heart **15**:209-228, 1930.

hands. Others had swelling and cyanosis of the fingers, as well as blanching, and in these the veins were invisible. The fingers of some began to appear puffed and cyanotic before blanching, suggesting that the veins were constricting before the arteries. All patients showed these phenomena in varying degree during an attack. In some of the patients the pain or discomfort accompanied arterial constriction. In other patients the pain and discomfort were associated only with the period of relaxation of arterial spasm. In the latter group pain was not associated with the vasoconstriction.

Again, it appeared that the difficulty in explaining these striking differences in the behavior of patients with Raynaud's disease had been due to failure to recognize that in some patients the symptoms are principally due to the fact that the veins are more readily constricted than the arteries. Also, it has not been recognized that in some of these patients the veins remain constricted while the arteries are relaxing, thus creating a state of vascular congestion. This explains the onset of puffiness as well as discomfort in the fingers in this group of patients during a period of arterial relaxation. This is only to be expected, since vessels that constrict more readily to a stimulus, as do the veins in this group of patients, not only constrict first but on removal of the stimulus relax last.

Although the walls of veins are thinner than the walls of the corresponding arteries, veins also are richly supplied by sympathetic nerve fibers.[4] The smooth muscle of the veins responds to nervous stimuli in the same manner as does the smooth muscle of arteries. Franklin's "Monograph on Veins," gives in detail the large body of experimental and clinical evidence demonstrating the important influence of the nervous system on the venous system. In 1839 Valentin [4] demonstrated contraction of the horse's abdominal vena cava by stimulation. Gobler [4] in 1850 found that under appropriate conditions the veins on the dorsum of the human hand responded to a tap by contraction. It was in 1864 that Goltz [4] showed the relationship of the nerves to the veins. Many physiologists have demonstrated and described the responses of both the superficial and the deep venous systems of the extremities to nervous stimuli.

Lewis and Landis during the years from 1929 to 1934, presented evidence that the attack of dead whiteness in the fingers or of cyanosis is due to a local fault in the wall of small arteries only, the digital and palmar arteries, so that they constrict abnormally in response to cold and to emotional upsets. They attempted to establish the fact that the veins do not participate in the abnormal vasoconstriction. Lewis [2]

4. Franklin, K. J.: A Monograph on Veins, Springfield, Ill., Charles C Thomas, Publisher, 1937.

discussed the observations of Weiss [5] and Barlow,[6] who presented clinical evidence that there is abnormal contraction in the veins.

Because our observations were so contrary to those of Lewis and of Landis we analyzed their evidence for concluding that only arterial spasm occurs in Raynaud's disease and that obstruction to venous outflow is not present. We reinterpreted their findings in the light of what we were seeing and in the light of what has been discovered concerning vein reflexes since their work done in 1930. We arrived at the conclusion that their own observations not only do not exclude venospasm but are compatible with its presence in Raynaud's disease.

Lewis dismissed Weiss's [5] conclusion that the veins participate in the abnormal vasoconstriction of Raynaud's disease. Lewis, to rule out the presence of venospasm, described 6 cases in which, he stated, the cyanosis of the fingers was replaced by blanching immediately after elevation of the extremities and again recurred after the extremities were dependent. This indicated to him the presence of patent venous channels in the arm and hand. To us, these observations could also be explained by the action of a vascular stretch reflex, as described by Doupe and others.[7] By this mechanism, elevation of the arms would cause a drop in venous pressure, removal of the stretch reflex and, therefore, venous relaxation, with relief of the cyanosis. If the arm should be returned to a dependent position, the stretch reflex would come into play again as a result of increased venous pressure. This would bring on venous constriction and would reestablish the cyanosis.

Although blood flow is greatly reduced, there is always sufficient arterial inflow in these patients to maintain the cyanosis. This explanation was not available to Lewis, since these vein reflexes were not described until a number of years after his investigations of Raynaud's disease.

Landis, in his microinjection studies of capillary pressure in Raynaud's disease,[3] stated that venospasm is not a factor in Raynaud's disease, as the capillary pressure in the fingers rises very little and very slowly in response to venous congestion induced by an increase in venous pressure as the result of a cuff around the upper part of

5. Weiss, M.: Ueber symmetrische Gangrän, Wien. Klinik **8**:346, 1882; Ueber Venenspasmus, Wien. med. Presse **23**:988, 1015, 1045 and 1095, 1882.

6. Barlow, T.: Three Cases of Raynaud's Disease, Tr. Clin. Soc. London **22**:413, 1888-1889; Some Cases of Raynaud's Disease, Illust. M. News **3**:73, 97, 125 and 176, 1889.

7. Doupe, J.; Robertson, J. S. M., and Carmichael, E. A.: Vasomotor Responses in the Toes: Effect of Lesions of the Cauda Equina, Brain **60**:281, 1937.

the arm. This phenomenon can as well be evidence of a mechanism at work during venospasm. If the veins are in spasm at the wrists, back pressure cannot be transmitted to the fingers from the brachial veins except through the venous plexus. Landis has stated that transmission of venous pressure to capillaries through these plexuses will cause but a small rise in capillary pressure in patients with Raynaud's disease. It is just such a small rise, 5 to 8 mm. of mercury, that he observed in a patient with Raynaud's disease, indicating that the transmission of back pressure from the arm to the fingers in his patient may have been referred only through these plexuses, the veins already being in spasm between the point of increased pressure and the capillaries of the cyanotic fingers. The fact that many patients do not have relief from venous spasm until after arterial spasm has ceased could also explain the appearance of slight swelling that was noted by Landis in the fingers during recovery from arterial spasm; this swelling he ascribed to "changes in fluid balance consequent upon asphyxia of the capillary wall and upon the increased capillary pressure." Landis also described a rise in capillary pressure during "the hyperemia" of recovery. Such a rise can be readily explained by venospasm causing engorgement of the capillaries, as in this phase arterial inflow would be continually increasing in the presence of a restricted outflow, although Landis chose to attribute this to capillary engorgement due to anoxia. However, as we have seen in a nonvasospastic but ischemic extremity, this swelling is not present, despite the appearance of rubor and capillary engorgement. Furthermore, these capillary studies do not explain the puffed fingers or hands at the beginning of an attack in some patients or the "puffed hands" that are present in others all winter.

Of the 10 patients with Raynaud's disease seen by us, the clinical features in only 1 were those produced by arterial spasm alone; in 8 both venospasm and arterial spasm were required to produce the picture and in 1 venospasm alone was present. The last was the patient with so-called cold allergy. The ages of the 10 patients ranged from 28 to 62 years; 9 were female and 1 was male. Necrosis of finger tips was present only in the group with both venous and arterial spasm. The probable explanation for this is that venous stagnation favors ulceration, just as it does in a leg with varicose veins or with thrombophlebitis.

In the 4 patients with Raynaud's phenomenon, the symptoms were part of a generalized scleroderma. In 2 of these patients there was evidence of both venous and arterial spasm, the veins being invisible and cyanosis and increased swelling being present when the patient was exposed to cold.

The following observations were made concerning the patients with both venospasm and arterial spasm:

1. The fingers of both hands blanched on exposure to cold or in response to emotional tension.

2. There was a history of puffed or swollen hands throughout the winter, in addition to blanching and cyanosis.

3. There was an appearance of cyanosis and swelling before blanching in some patients.

4. Fingers were puffed during as well as between attacks.

5. Increased swelling followed the termination of attacks.

6. Veins on the dorsa of the hands were invisible or inconspicuous during exposure to cold and in most of these patients even during exposure to warmth.

On the basis of our observations we formulated the following classification which includes all the characteristic clinical pictures seen in patients with Raynaud's disease and Raynaud's phenomenon. It is obvious that the clinical picture will vary depending on the intensity of constriction in arteries and in veins and on the type of vessel in which abnormal constriction predominates.

Classification of Raynaud's Group of Vasospastic Disorders
(Bilateral, Symmetric, Digital Involvement)

1. Arterial spasm (or predominantly arterial); blanching, with or without cyanosis (no swelling)
   (*a*) Raynaud's disease: arterial (primary—no obvious cause)
   (*b*) Raynaud's phenomenon: arterial (secondary—due to other conditions)
2. Arterial and venous spasm (mixed); blanching, cyanosis and swelling
   (*a*) Raynaud's disease: arterial and venous (primary—no obvious cause)
   (*b*) Raynaud's phenomenon: arterial and venous (secondary—due to other conditions)
3. Venospasm (or predominantly venous); swelling and cyanosis (blanching absent or slight)
   (*a*) Raynaud's disease: venous (including some cases of "cold allergy")

REPORT OF CASES

CASE 1.—*Raynaud's disease; mixed venospasm and arterial spasm.*

A 49 year old woman was well until the fall of 1942, when she began to have blanching, cyanosis, coldness and puffiness in all the fingers and thumbs on exposure to cold or with nervous tension. The same signs were present in the toes in a milder form. These manifestations started shortly after a daughter had encephalitis in 1941. The hands had been unusually cold for some years prior to the onset of the other signs. During the winter of 1942-1943 she experienced cracking of the skin of the left index and right fourth fingers. Numbness and tingling of the fingers accompanied the attacks of vasospasm. The patient felt very tired and nervous and complained of flushes for the past six years. She had not been helped by being told by a physician that gangrene

of the hands might develop. She also had a history of paroxysmal tachycardia for the past twenty years. One ovary and the uterus had been removed for fibroids in 1938.

Physical examination when she was first seen in December, 1944, disclosed all the fingers to be puffed but not blanched or cyanotic. The veins on the dorsa of the hands were small but visible. All pulses were palpable at the wrists and oscillometric readings were low normal. When the vascular tone test was done, however, during the period of cooling the veins on the dorsa of the hands constricted and became invisible. During this period the hands became blanched, then ruborous and then rapidly cyanotic. The fingers became very puffy during this period. When heat was applied to the trunk, the veins on the hands gradually dilated and the fingers assumed a normal color. The fingers were less swollen but still had a puffed appearance. The rest of the physical examination revealed no definite abnormalities. The blood pressure was 128 systolic and 88 diastolic. The throat, neck, heart, lungs, abdomen and spine were normal. The basal metabolic rate was —12 per cent. Roentgenologic examination of the hands showed nothing abnormal.

This swelling of the fingers, together with blanching and cyanosis, was present in varying degree in 8 of the 10 patients with Raynaud's disease. In most of these patients the veins on the dorsa of the hands were invisible even while there was vasodilatation.

CASE 2.—*Raynaud's disease; arterial spasm.*

A 47 year old woman had begun to have dead white fingers on exposure to cold and with emotional tension three years previously. Cyanosis was usually intermingled with the pallor. On return to a warm environment the hands became red. There was no swelling. Numbness and tingling also occurred during the attack. Her hands and feet have been cold all of her life. A hysterectomy had been performed when the subject was 20 years old.

On examination, all pulses at the wrists and ankles were palpable. Oscillometric readings were on the low side of normal. The hands and feet were cold. A reactive hyperemia test disclosed no signs of organic digital arterial occlusion. Placing the left hand in ice water brought on blanching of the distal phalanges and slight blanching of the proximal phalanges. The fingers had no signs of puffiness. The ridges in the skin on the fingers were all plainly visible. The veins on the dorsa of the hands were prominent while there was vasodilatation and were definitely visible even when constricted.

It is interesting that this was the only patient of the 10 seen by us in whom arterial spasm alone appeared to be present. Venospasm as well as arterial spasm was present in all the others except the patient with so-called cold allergy, in whom venospasm occurred alone.

COMMENT

The confusion that exists in interpreting the series of events in patients with Raynaud's disease and with Raynaud's phenomenon has arisen, we believe, from failure to consider that the veins often partake in the pathologic spasm. It is of interest that Raynaud himself [8]

8. Raynaud, A. G. M.: De l'asphyxie locale et de la gangrène symmétrique des extrémités, Paris, Rignoux, 1862.

described a type of digital spasm in which veins must have been involved. In observation II, he gave this description: "Madame X, 25 years old, . . . has been very subject for a long time to having dead fingers. These become in an instant the seat of coldness, pallor and absolute insensibility . . . The fingers presented a very peculiar conformation. They were extremely large and soft, the hands themselves appeared edematous and they formed a very striking contrast with the slender wrists and forearms."

It is well known that a variety of pathologic states are created as a result of venospasm. The severe edema that may occur in thrombophlebitis has been recognized as often being caused by the constriction of many veins in the extremity as the result of reflexes set up in the one segment of vein which is inflamed and in a state of irritability. It is also recognized that the venous congestion that occurs in thrombophlebitis initiates reflex arterial constriction. This appears to be a necessary reflex to prevent the continued swelling of the extremity which would occur if the arteries remained dilated. This useful reflex tends to prevent extreme edema when veins are obstructed or in spasm. It has also been shown that simply congesting the veins in one extremity causes widespread changes in tone of both arteries and veins in the contralateral as well as in the same extremity.

It is our impression that this reflex may be a basic factor in inducing the arterial spasm in some patients with Raynaud's disease. The appearance of cyanosis and puffiness at the beginning of an attack in some patients suggests that venospasm occurs first, and that then, with distention of venules and capillaries distal to the spastic veins, reflex arterial constriction is initiated to prevent the swelling and congestion that would occur if the arteries remained unconstricted or dilated. An anatomic factor that fits into this concept of what may be happening in some patients with Raynaud's disease is that the veins in the hands are more superficially placed and are the first to be exposed to a stimulus such as cold.

Venous reflexes play an important role in certain physiologic processes. One of the mechanisms in the regulation of the circulation when a person assumes the erect posture is initiated by incipient distention of the veins.[9] This stretch reflex has been found to act as a stimulus to the production of arterial constriction in the lower extremities while a person is in the upright position, to prevent the dumping of too much blood into the legs. The process of frequent turning in bed during sleep is a result of an irritative reflex set up in veins as blood accumulates in them when no muscular movement occurs. Finally,

9. Jackson, M. M.: Anticipatory Cardiac Acceleration During Sleep, Science **96**:564, 1942.

when there is sufficient venous distention a reflex is set in motion which makes a person turn and move the muscles which massage the blood out of the veins.[9]

Thus far, mention has been made only of an exaggerated constriction of veins and arteries to cold and emotional tension as an explanation of the clinical picture in Raynaud's disease and in Raynaud's phenomenon. However, one other factor must be considered, the possibility that in some of these patients the capacity for venous outflow is not as great as it should be in relation to the capacity for arterial inflow. It is possible that there may be an imbalance between arterial and venous flow. We have observed, as have many others, the great variation in the caliber of veins in the hands and arms in different persons. Many of the patients with Raynaud's disease have small veins. A disproportion in the caliber of arteries and veins may in itself largely explain the cyanosis and puffiness. This is confirmed by the fact that cyanosis persists after sympathectomy in patients with Raynaud's disease, and may even increase, as in a patient mentioned by Lewis.[2] In these patients blanching (due to spasm) has been alleviated by sympathectomy, but the remaining cyanosis is explained by this basic anatomic disproportion between arteries and veins. This is further confirmed by the fact that Fulton's patient (described by Lewis) had an increase in cyanosis in the early morning following a probable period of vasodilatation during sleep. One of our patients, on whom sympathectomy was performed chiefly because of severe pain, behaved in a similar manner. There was relief of the pain following sympathectomy, but she continued to have puffy, cyanotic fingers, although the fingers no longer blanched. We do not see how this can be explained on any other basis than of a disproportion in arterial and venous capacity, since sympathectomy was performed on both arteries and veins.

It has been suggested by Hunt[10] that true Raynaud's disease is rare and that most patients who are seen with vasospastic phenomena in the hands have Raynaud's phenomenon. Lewis[2] has suggested that the term "Raynaud's disease" should be dropped entirely. Still others have expressed differing views as to what should be called Raynaud's disease and what should be called Raynaud's phenomenon.

It is our feeling that if the connotation of severity attached to the term "Raynaud's disease" is removed both terms are useful. We have found that a tendency to an exaggerated constriction of digital vessels is not uncommon. We know that there is a tremendous range in vascular tone in the hands of normal persons. Failure to realize that there is also a wide range in abnormal digital constriction to cold

10. Hunt, J. H.: Raynaud Phenomena: Critical Review, Quart. J. Med. **5**:399, 1936.

and emotional tension has given an undeservedly serious connotation to the diagnosis of Raynaud's disease. The great majority of these persons have only mild symptoms, which do not increase in severity. It is only those with the severest grades of digital vasoconstriction who require sympathectomy. Only 3 of 10 patients with Raynaud's disease had small necrotic lesions at the finger tips, and of these only 1 required bilateral upper thoracic sympathectomy. Sympathectomy is indicated only in the presence of severe symptoms and beginning necrosis. The others were all treated conservatively, with special emphasis on reassurance. In the milder forms of Raynaud's spasm, reassurance is sufficient, together with mild vasodilator therapy. Many of these patients are frightened by the diagnosis of Raynaud's disease. When it is explained to them that they have simply a mildly exaggerated vascular response to cold and to emotional tension, their dread of gangrene is usually allayed, and this in itself reduces the tendency to vasoconstriction. It must be remembered that the emotional stimulus is present constantly in these patients, whereas the stimulus of cold can be removed. Treatment directed toward reducing nervous tension is extremely necessary, and reassurance as to the nature of the condition is of paramount importance. Mufson [11] has emphasized the role of psychic factors in Raynaud's disease. His article points out that in some patients only the removal of the cause of severe nervous tension will prevent attacks. We have seen the first attack of dead whiteness in the fingers precipitated in several patients by a severe emotional shock, such as the death of a member of the family. We have been impressed by the presence of factors that maintain a high degree of nervous tension in practically all patients with Raynaud's disease.

The program of management also includes, of course, avoidance of exposure to severe cold, wearing of warmer clothing than that worn by the average person, taking of a warm tub bath daily in a warm bathroom, abstinence from tobacco and use of an adequate diet. We have also found thyroid of value, since even a slightly reduced basal metabolic rate will aggravate a tendency to peripheral vasoconstriction in response to cold. Estrogen therapy is useful when Raynaud's disease occurs during the menopause. Vasodilators such as mecholyl bromide we have found of only occasional benefit. We reserve sympathectomy for the occasional case of severe type, in which the disease is obviously progressing and digital necrosis is beginning to develop. We have never seen the loss of even part of a digit from Raynaud's disease. One must, of course, rule out thromboangiitis obliterans in the presence of digital gangrene.

11. Mufson, I.: The Mechanism and Treatment of Raynaud's Disease: A Psychosomatic Disturbance, Ann. Int. Med. **20**:228, 1944.

The term "Raynaud's phenomenon" should be reserved for digital vasospasm, secondary to other known pathologic conditions. Conditions in which secondary digital vascular spasm occurs include scleroderma, cervical rib, scalenus anticus syndrome, pneumatic hammer disease, arthritis, various neurologic diseases, pressure from a crutch, causalgia and probably other diseases.

It should be noted that we have limited the terms "Raynaud's disease" and "Raynaud's phenomenon" to bilateral, symmetric digital involvement. Where vasospasm is present in one extremity it should be called simple vasospasm. There is usually a local explanation, either in the extremity or in the spine, for such unilateral vasoconstriction.

SUMMARY

Observation of 10 patients with Raynaud's disease and 4 patients with Raynaud's phenomenon has disclosed evidence that spasm of the veins as well as of the arteries is present in the majority of these patients. Arterial spasm alone cannot explain the clinical picture in most patients.

In some patients venospasm may predominate over arterial spasm. The clinical features in each patient will vary depending on which part of the vascular tree is predominantly involved in the abnormal vasoconstriction.

It is suggested that in some patients with Raynaud's disease the clinical picture is influenced by an anatomic disproportion in capacity between arterial and venous flow.

On the basis of clinical observations of these patients during the test for basal vascular tone, a classification has been made to clarify the terms "Raynaud's disease" and "Raynaud's phenomenon."

Raynaud's disease is not rare. The milder forms are fairly common and do not deserve the connotation of seriousness usually associated with the diagnosis. Reassurance is an important part of treatment.

In a patient with so-called cold allergy venospasm was found to develop on exposure to cold without development of arterial constriction, which explained the development of cyanosis and pronounced swelling without blanching.

PURPURIC MANIFESTATIONS OF HEATSTROKE

Studies of Prothrombin and Platelets in Twelve Cases

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THE appearance of purpuric manifestations in heatstroke has been recorded by several authors.[1] According to Wakefield and Hall,[2] Andnal gave the first accurate account of the major postmortem features in 1838—namely, petechiae, liquid blood and venous engorgement. In 1892 Osler [3] wrote: "The venous engorgement is extreme, particularly in the cerebrum. The blood is usually fluid; the lungs are intensely congested. Parenchymatous changes occur in the liver and spleen."

In a review of available literature concerning heatstroke we have not found an adequate explanation of this hemorrhagic phenomenon. However Wilson and Doan [4] reported decreases in prothrombin and platelets in patients subjected to artificially induced fever. They concluded that the decrease in prothrombin was secondary to hepatic damage and that the degree of thrombopenia depended on the extent of megakaryocytic damage.

The purpose of this report is to record the results of repeated determinations of prothrombin time and platelet counts on 12 patients critically ill with heatstroke and to point out evidence suggesting that an increase in capillary permeability occurs.

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1. (*a*) Gauss, H., and Meyer, K. A.: Heat Stroke: Report of One Hundred and Fifty-Eight Cases, Am. J. M. Sc. **154**:554, 1917. (*b*) Wilcocks, C.: Effects of Heat in Persia and Iraq, Trop. Dis. Bull. **41**:74 (Jan.) 1944. (*c*) Wilson, G.: The Cardiopathology of Heatstroke, J. A. M. A. **114**:557 (Feb. 17) 1940.

2. Wakefield, E. G., and Hall, W. W.: Heat Injuries, J. A. M. A. **89**:92 (July 9) 1927.

3 Osler, W.: Principles and Practice of Medicine, New York, D. Appleton and Company, 1892, p. 1017.

4. Wilson, S. J., and Doan, C. A.: The Pathogenesis of Hemorrhage in Artificially Induced Fever, Ann. Int. Med. **13**:1214 (Jan.) 1940.

The Quick method[5] using undiluted plasma was the procedure employed in all determinations of prothrombin time. Simultaneous and identical tests were performed on normal plasma. Bacto-thromboplastin[6] was used in all tests and controls. Clot formation is obtained in twelve to fourteen seconds with this thromboplastin preparation and normal undiluted plasma. Clot formation occurred in most of our controls in fourteen seconds. Since all control tests were on normal undiluted plasma we recorded prothrombin time in seconds instead of in per cent of normal.

All platelet counts were made by the direct method of Rees and Ecker.[7] The normal count by this method is 200,000 to 500,000.

The hyperpyrexia was reduced by a routine method consisting of continuous water sponges, brisk massage of the trunk and extremities and directing electric fans on the patient.

TABLE 1.—*Laboratory and Clinical Observations*

Case number	1	2	3	4	5	6	7	8	9	10	11	12
On Admission												
Temperature	110	109	108	110	110	110	110	110	110	110	106	106
Unconsciousness	+	+	+	+	+	+	+	+	+	+	—	—
Dry skin	+	+	+	+	+	+	+	+	+	+	+	+
Blood pressure	130/60	136/90	132/84	125/70	136/90	130/80	90/60	100/60	120/90	?/?	?/?	132/80
Cyanosis	+	+	+	+	+	+	+	+	+	+	0	0
Petechiae	+	+	+	+	+	+	+	h+	+	m—	—	—
Prothrombin time (sec.)	14	20	14	?	16	17	30	16	16	15	14	17
Platelets (thousands)*	80	68	?	?	92	40	?	104	120	?	80	63
Subsequently												
Incontinence	+	+	+	+	+	+	+	+	+	+	—	—
Convulsions	+	+	0	+	+	0	—	0	—	—	—	—
Decreased capillary tone	+	+	+	+	+	+	+	+	?	?	—	—
Vomiting	+	+	+	?	+	+	+	+	+	+	+	+
Rales and rhonchi	+	+	+	+	+	+	+	?	+	+	+	—
Petechiae	+	+	+	+	+	+	h+	h+	+	m+	—	—
Prothrombin time (sec.)†	38	35	30	108	20	20	30	20	?	?	17	17
Platelets †	40	68	85	70	31	35	?	?	?	?	50	30
Bleeding time (min.)†	12	4¼	3	10	6	9	?	?	?	?	3	3
Icterus index †	47	9	31	+?	15	?	?	?	?	?	9	?
Died (hours survived)	..	..	..	72	288	..	6	9½	5½	5½		

* Maximum deviation from normal for the twenty-four hour period.
† Maximum deviation from normal during the illness.
The letter h indicates hematemesis. The letter m indicates melena.

Laboratory and clinical observations are summarized in table 1, and a brief clinical report of the facts germane to the hemorrhagic phenomena is given for each case.

REPORT OF CASES

CASE 1.—A white man aged 31 was admitted to the hospital at 5:30 p. m. on Sept. 6, 1944, with a temperature of 110 F. He was deeply cyanotic, uncon-

5. Quick, A. J.: Nature of Bleeding in Jaundice, J. A. M. A. **110**:1658 (May 14) 1938; Prothrombin in Preserved Blood, ibid. **114**:1342 (April 6) 1940.

6. A product of Difco Laboratories, Detroit, Mich.

7. Kracke, R. R., and Parker, F. P.: A Textbook of Clinical Pathology, Baltimore, Williams & Wilkins Company, 1940, p. 130.

scious and restless and was having recurrent generalized convulsions. The blood pressure was 130 systolic and 60 diastolic. The skin was hot and dry, and many petechiae were noted. Rales and wheezes were heard throughout both lungs. All deep reflexes were absent. The temperature was reduced to 101 F. within one hour. His blood pressure fell to 80 systolic and 60 diastolic soon after his admission but was restored to its previous level after an infusion of 500 cc. of plasma. The prothrombin time was fourteen seconds. The platelet count was 80,000.

On September 7, consciousness had returned and the patient's general appearance was good. The lungs were much clearer. However, there was a noticeable increase in the number of petechiae. The prothrombin time was twenty-three seconds, and the platelet count was 28,000.

On September 8, he continued to improve. The prothrombin time was thirty-eight seconds, platelet count 72,000, bleeding time ten minutes and forty seconds and icterus index 25.

On September 9, the lungs were clear. The prothrombin time was thirty-six seconds, platelet count 66,000, bleeding time twelve minutes and icterus index 47.

On September 10, he appeared well. The prothrombin time was nineteen seconds, platelet count 52,000 and bleeding time twelve minutes.

On September 11, the prothrombin time was eighteen seconds, platelet count 146,000, bleeding time six minutes and icterus index 57.

On September 13, the prothrombin time was fourteen seconds, platelet count 130,000, bleeding time eight minutes and icterus index 47.

On September 15, the platelet count was 120,000 and the bleeding time five minutes and fifty seconds.

On September 17, the platelet count was 298,000, bleeding time four minutes and icterus index 17.

The convalescence was uneventful.

CASE 2.—A white man aged 23 was admitted to the hospital July 19, 1944, with a temperature of 110 F. He was cyanotic, unconscious, vomiting and incontinent of urine and feces. The blood pressure was 136 systolic and 90 diastolic. The skin was dry, and petechiae were present on the abdomen and thorax. Large conjunctival hemorrhages were present in both eyes. All deep reflexes were absent. The temperature was reduced to 103 F. in less than three hours. The prothrombin time was fifteen seconds on his admission and a few hours later was twenty seconds. The platelet count was 68,000.

On July 20, he remained unconscious and critically ill. The prothrombin time in the morning was nineteen seconds, and when the determination was repeated in the afternoon it was twenty-eight seconds. The icterus index was 19, platelet count 68,000 and bleeding time four minutes and fifteen seconds.

On July 21, he regained consciousness but remained stuporous and confused throughout the day. The prothrombin time was thirty-five seconds.

On July 22, he was more alert but was unable to find the correct words to express himself. The prothrombin time was eighteen seconds.

On July 23, he seemed much improved. It was recorded that he was ataxic. The icterus index was 9, and the oral hippuric acid test showed 68 per cent normal excretion.

On July 24, the prothrombin time was fourteen seconds, and the platelet count was 200,000.

His recovery was slow and uneventful except for the ataxia, which persisted in some degree for three weeks.

CASE 3.—A white man 36 years of age was admitted to the hospital July 29, 1944, with a temperature of 108 F. He was cyanotic, unconscious and incontinent. Many petechial hemorrhages were noted in the conjunctivas and on the abdomen. chest and extremities. The deep reflexes were greatly diminished. Rhonchi and rales were heard throughout both pulmonary fields. His temperature was reduced to 101 F. in four hours, and consciousness returned in six hours. The prothrombin time was fourteen seconds on his admission; a few hours later it was nineteen seconds.

On July 30, the maximum temperature was 101 F. The lungs were clear. The prothrombin time was twenty-seven seconds in the morning and thirty seconds in the afternoon.

On July 31, the maximum temperature was 101.4 F. The prothrombin time was twenty-three seconds, icterus index 25, bleeding time three minutes and platelet count 85,000.

On August 1, he no longer appeared acutely ill. The maximum temperature was 100.6 F. The prothrombin time was nineteen seconds, platelet count 85,000 and bleeding time normal.

On August 2, the prothrombin time was fifteen seconds, platelet count 132,000 and bleeding time normal. The icterus index was 31.

The remaining course was uneventful; the icterus index was 17 on August 5 and 10 on August 8. The platelet count was 268,000 on August 6.

CASE 4.—A white youth 18 years of age was admitted to the hospital at 7 p. m. on May 19, 1943, with a temperature of 110 F. He was unconscious; the skin was dry, and petechiae were noted. The temperature was reduced to 101 F. in two hours.

On May 20 showers of petechiae appeared on the extremities and trunk. The prothrombin time was forty-nine seconds. Five milligrams of menadione (vitamin K) was given parenterally, and the dose was repeated every six hours. The prothrombin time was one hundred and eight seconds, bleeding time ten minutes and platelet count 90,000 six hours after the first dose of the vitamin K preparation.

On May 21, the prothrombin time was seventy-two seconds, and the platelet count was 70,000. He was conscious and cooperative and answered questions readily. The improvement lasted only a few hours. There was an increase in temperature as well as in respiration and pulse rate. Evidence of an area of consolidation in the right lung was detected and confirmed by roentgenogram. A previous roentgenogram had been normal. A transfusion of 500 cc. of whole blood was given and was repeated during the night.

On May 22, the patient died at 6 a. m.

The pathologic diagnoses included mild diffuse icterus, petechiae of the skin, mild diffuse hemorrhage in the myocardium, severe multiple interstitial pulmonary hemorrhages, multiple petechial hemorrhages in the stomach and intestines, multiple small hemorrhages in the pancreas and spleen, multiple diffuse perivascular hemorrhages in the brain, moderately severe fatty degeneration of the liver and pneumonia with consolidation in the upper lobe of the right lung and a separate consolidation in the middle portion of the lower lobe of the right lung.

CASE 5.—An obese white man, 25 years of age, was admitted to the hospital Sept. 6, 1944, with a temperature of 110 F. He was unconscious, cyanotic, vomiting and incontinent. The blood pressure was 130 systolic and 90 diastolic. The skin was dry, and petechiae were present on the abdomen, chest and arms.

Rales and rhonchi were heard throughout both lungs. The deep reflexes were absent. His temperature was reduced to 100.4 F. in three hours. He had several generalized convulsive seizures during the first few hours. A few minutes after his admission the prothrombin time was sixteen seconds, and the platelet count was 108,000. A few hours later the platelet count was 92,000 and the prothrombin time twenty seconds.

On September 7, he remained unconscious and cyanotic. The blood pressure was 92 systolic and 50 diastolic. Hemorrhages in the eyes and skin were more prominent. The prothrombin time was eighteen seconds, platelet count 44,000 and bleeding time four minutes and fifty seconds.

On September 8, his unconsciousness continued. A transfusion of 400 cc. of whole blood was given. The platelet count was 31,000 and the bleeding time was three minutes. The prothrombin time was fourteen seconds and remained normal until the day of his death.

On September 9, he remained critically ill. Rales and rhonchi were present throughout both pulmonary fields. The platelet count was 78,000.

On September 10, a transfusion of 500 cc. of whole blood was given. The platelet count was 66,000, and the bleeding time was six minutes.

On September 11, he regained consciousness but was unable to speak. The bleeding time was six minutes and ten seconds, platelet count 168,000 and icterus index 15.

On September 12, 13, 14 and 15, there was slight improvement. Daily platelet counts were 94,000, 130,000, 178,000 and 140,000, respectively. The bleeding time varied from six to eight minutes. Once every twenty-four hours his temperature would rise to 107 or 108 F. but was promptly controlled by cool water sponges.

On September 16, his temperature did not exceed 104 F., and he seemed to be doing well.

On September 17, an acute pulmonary edema developed late in the afternoon, and the patient died at 6:30 p. m. The prothrombin time was sixteen seconds, and the platelet count was 260,000, about eight hours before death.

The pathologic diagnoses were: petechiae in the skin of the trunk, severe multiple pulmonary hemorrhages, severe bilateral pulmonary edema, acute early bronchopneumonia, severe acute purulent bronchitis, small mucosal hemorrhages of the large and small intestines, multiple small petechial hemorrhages of the subarachnoid spaces and necrosis of the liver.

In this case the prothrombin index was normal except for a slight deficiency during the first forty-eight hours and on the day of death. This is of particular interest because the most outstanding pathologic change was a severe central necrosis of the liver in which approximately 60 per cent of the parenchyma was destroyed. Conclusive evidence of megalokaryocytic damage could not be demonstrated in postmortem smears of bone marrow.

CASE 6.—A white man aged 26 was admitted to the hospital Sept. 5, 1944, with a temperature of 110 F. He was unconscious, cyanotic, vomiting and incontinent. The blood pressure was 130 systolic and 80 diastolic. The skin was dry. Petechiae were present on the trunk, and bilateral conjunctival hemorrhages were observed. Rales and rhonchi were heard throughout both lungs. Deep reflexes were present but extremely weak.

The blood pressure dropped to 80 systolic and 50 diastolic, but the systolic pressure rose to 106 after an infusion of 500 cc. of plasma.

The prothrombin time was seventeen seconds, and the platelet count was 40,000 a few minutes after his admission.

On September 6, rales and respiratory wheezes could be heard throughout both lungs. Late in the morning consciousness returned. The prothrombin time was twenty seconds; the platelet count was 80,000 in the morning and 40,000 late in the afternoon.

On September 7, no additional petechiae were noted. Deep reflexes had improved. Prothrombin time was twenty seconds, platelet count 35,000 and bleeding time four minutes and thirty-five seconds.

On September 8, he was greatly improved. The prothrombin time was normal, platelet count 50,000 and bleeding time six minutes. A hippuric acid test (oral) showed 37 per cent normal excretion.

On September 9, the platelet count was 72,000, and the bleeding time was four minutes and thirty seconds.

On September 10, he appeared well. The prothrombin time was eighteen seconds, platelet count 82,000 and bleeding time nine minutes.

On September 11, the prothrombin time was normal, platelet count 132,000 and bleeding time six minutes.

His recovery was slow but without special event. The platelet count had increased to 238,000 by September 13.

Case 7.—A white man 27 years of age was admitted to the hospital June 17, 1944, with a temperature of 110 F. He was unconscious, cyanotic and incontinent. The blood pressure was 90 systolic and 60 diastolic. All deep reflexes were absent. Petechiae were noted on the chest and about the ankles. He vomited a small amount of blood.

He grew progressively worse and died six hours after his admission. The prothrombin time soon after his admission was thirty seconds.

The pathologic diagnoses were: petechial hemorrhages in the skin, moderate subepicardial and subendocardial hemorrhage and severe multiple bilateral pulmonary hemorrhages. (The right lung weighed 760 Gm. and the left 1,100 Gm.) Pulmonary hemorrhages were a contributory cause of death.

Case 8.—A white man aged 25 was admitted to the hospital Sept. 5, 1944, with a temperature of 110 F. The blood pressure was 100 systolic and 60 diastolic. He was cyanotic, unconscious and incontinent. All deep reflexes were absent.

Four hours after admission he vomited a large amount of blood. Purpuric spots were noted on the trunk. About nine hours after his admission the systolic blood pressure fell to 70; the cyanosis became intense, and the patient died.

The prothrombin time was sixteen seconds on his admission; eight hours later it was twenty seconds. The platelet count was 104,000.

The pathologic diagnoses were: petechial hemorrhages in the skin, subendocardial hemorrhage on the left surface of the intraventricular septum, massive pulmonary hemorrhage of the right lung (weight 1,640 Gm.) and a smaller amount in the left lung (weight 500 Gm.) and hemorrhage of the gastric mucosa.

Case 9.—A white man 37 years of age was admitted to the hospital July 18, 1944, with a temperature of 110 F. He was unconscious and deeply cyanotic. The blood pressure was 120 systolic and 90 diastolic. The pulse was rapid and of poor volume. He became progressively worse and died six hours after his

admission. The prothrombin time was sixteen seconds. The platelets numbered 120,000 soon after his admission.

The pathologic diagnoses were: petechial hemorrhages in the skin, subepicardium, gastric mucosa, small and large intestines, pancreas and subendocardium of left intraventricular surface; massive bilateral pulmonary hemorrhage; moderate pulmonary edema (the right lung weighing 1,360 Gm. and the left 1,000 Gm.), and mild cerebral edema.

CASE 10.—A white man 21 years of age was admitted to the hospital July 18, 1944, with a temperature of 110 F. He was unconscious, cyanotic and incontinent and was vomiting. The pulse was rapid and of poor volume. The blood pressure reading was unobtainable. Rhonchi and rales were heard throughout both lungs. He was given a 500 cc. infusion of plasma.

Three hours after his admission the systolic blood pressure was 40 mm. of mercury. A few minutes after his admission the prothrombin time was normal. Five hours after admission he passed a large bloody stool and died thirty minutes later.

The pathologic diagnoses were: severe generalized dehydration, severe generalized passive congestion, multiple mild pulmonary atelectasis (weight of right lung 800 Gm. and of left lung 600 Gm.), mild subepicardial hemorrhages, superficial subendocardial hemorrhage of the left side of the intraventricular septum and severe gastrointestinal hemorrhage.

CASE 11.—A white youth aged 18 was admitted to the hospital Aug. 30, 1944. His temperature was 106 F. He was conscious but confused. The skin was dry, but no petechiae were noted. The lungs were clear; deep reflexes were present and equal. The temperature was reduced to 100.6 F. in three hours. His recovery was rapid and uneventful. The prothrombin time on his admission was fourteen seconds and a few hours later seventeen seconds. The platelets numbered 302,000 on his admission and a few hours later 80,000.

On August 31, the platelet count was 88,000. The prothrombin time and bleeding time were normal.

On September 1, the platelet count was 50,000; the prothrombin time and bleeding time remained normal. The icterus index was 9.

On September 2, the platelet count was 108,000, and the icterus index was 9. The oral hippuric acid test showed 44 per cent normal excretion.

CASE 12.—A white man aged 35 was admitted to the hospital Sept. 6, 1944, with a temperature of 106.4 F. He appeared weak and apprehensive, but he was mentally alert. The blood pressure was 132 systolic and 84 diastolic. The skin was dry, but no petechiae were noted. The deep reflexes were present and equal. The temperature was reduced to 101 F. in one hour. The initial prothrombin time was seventeen seconds; other repeated determinations were normal. The platelet count on his admission was 63,000 and a few hours later 30,000. The second day the platelet count was 130,000, the third day 135,000 and the fourth day 158,000. The bleeding time did not exceed three minutes. His recovery was rapid and uneventful.

COMMENT

Decrease of capillary tone or elasticity could be demonstrated in the severely ill patients by inflating a blood pressure cuff to a point midway between the systolic and the diastolic pressure. Distal to the constriction a striking mottled cyanosis appeared and persisted from three to five

minutes after the constriction was released. This could be demonstrated for several days in patients who survived, disappearing about the time the patient resumed sweating. It may be that the physiologic capillary dilation that occurs on exposure to high environmental temperature reaches a pathologic state, permitting red cells and plasma to extravasate. Such an increase in capillary permeability would explain the presence of petechiae in cases 8 and 9 on the patients' admission, when the prothrombin times were sixteen seconds and the platelet counts were more than 100,000. This slowly disappearing mottled cyanosis distal to the constriction could not be demonstrated in the 2 mildly ill patients (cases

TABLE 2.—*Observations at Necropsy*

Case number	4	5	7	8	9	10	A*	B*	C*	D*	Total Cases
Bronchopneumonia	3+	2+	1+	...	...	...	...	...	...	...	3
Pulmonary edema	...	4+	...	...	...	...	...	...	...	2+	2
Atelectasis	...	2+	...	...	...	3+	...	...	1+	...	3
Necrosis of liver	3+	3+	...	...	...	...	...	...	...	...	2
Hemorrhage:											
Pulmonary	3+	4+	3+	3+	3+	2+	2+	2+	3+	2+	10
Skin	4+	2+	3+	4+	3+	...	...	2+	1+	3+	8
G. I. mucosa	3+	2+	...	2+	3+	2+	...	...	2+	2+	7
Subepicardial	...	2+	3+	...	2+	2+	...	1+	...	3+	6
Myocardial	...	...	...	...	...	...	1+	...	...	...	1
I. V. septum †	...	...	3+	4+	3+	2+	...	4+	3+	3+	7
Subarachnoid	2+	2+	...	...	...	...	3+	2+	...	...	4
Brain (perivascular)	2+	...	1+	...	...	2+	...	...	...	...	3
Pancreatic	2+	...	...	3+	...	...	...	...	...	...	2
Diaphragmatic	...	...	...	...	...	...	...	2+	...	...	1
Mediastinal	2+	...	...	...	...	...	...	...	...	...	1
Splenic	2+	...	...	...	...	...	...	...	...	...	1
Hepatic	...	...	...	...	...	...	...	...	2+	...	1
Coalescence of RBC in cerebral capillaries	...	...	...	3+	...	...	2+	...	2+	...	3
Survival in hours	72	288	6	9.5	5.5	5.5	1	11.5	3	0.3	

* Protocols available but not included in this study.
† Subendothelial hemorrhage in intraventricular septum.

11 and 12), whose temperatures did not exceed 106.4 F., indicating that capillary damage was not so profound. This would explain why petechiae did not appear in these 2 mildly ill patients when the platelets numbered 30,000 and 50,000. Therefore, it seems plausible to postulate that, in addition to a decrease in prothrombin time and/or platelet count, a third factor, namely, capillary damage, contributes to the pathogenesis of the hemorrhagic manifestations of heat stroke.

Table 2 summarizes the pathologic observations. The location and severity of the purpuric manifestations are indicated. Four protocols in addition to the reports of cases presented here were available for review and have been included in this table.

The significance of this hemorrhagic phenomenon is not easily evaluated. The actual volume of blood lost was not sufficient to cause death, and the patient in case 3 was the only one in whom the amount lost was a valid contribution to the cause of death. The mechanical effect of the pulmonary hemorrhage was a serious complication in cases 4, 5, 7, 8 and 9. Wilson [1c] reported subendocardial hemorrhage in 1 case of sunstroke and in 3 cases of uncontrollable hyperpyrexia resulting from artificial fever therapy. He concluded: "The most striking and probably the actual fatal mechanism is a rather extensive hemorrhage under the endocardium of the left ventricle especially in the septal wall in the region of the bundle of His." We were not aware of this report at the time we observed these patients, and special studies to determine damage to the conduction system were not made. However, subendothelial hemorrhage in the intraventricular septum was recorded in 7 of the 10 available protocols reviewed and included in table 2. The survival time of the 7 patients varied from a few minutes to eleven hours. Electrocardiographic studies were impractical in examination of these patients owing to spasticity, muscular fibrillation, convulsions or purposeless movement. Conduction defects were not demonstrated electrocardiographically in patients who survived. It is unfortunate that we were not able to determine the number of platelets and the prothrombin activity just prior to death in the 4 patients who survived less than ten hours.

The extensive hepatic damage found at necropsy in cases 4 and 5 plus the abnormal results of the hippuric acid tests in the 3 cases in which they were performed are evidence that the decrease in prothrombin is due to hepatic damage. The elevated icterus indexes also suggest hepatic damage. However, the icterus may have been due in part to absorption of extravasated blood. Therefore, therapy should be directed to the prevention of damage to the liver—namely, intravenous administration of dextrose, vitamins, choline chloride and liberal amounts of protein and carbohydrates with a minimal amount of fat.

Smears of bone marrow obtained at necropsy and, in 1 case, shortly before death did not reveal unequivocal evidence of megalokaryocytic damage.

To become enthusiastic about therapeutic correction of the prothrombin and/or platelet deficiency, one would have to disregard three very important facts: 1. Heatstroke is not infrequently fatal in a few minutes or a few hours. 2. The quantity of blood lost is not the primary cause of death, and the part played by extravasation of plasma through the capillaries is an unknown quantity. 3. Hemorrhage in the lungs, myo-

cardium and elsewhere that might be of importance owing to the mechanical effect may occur too rapidly for therapy to be of value.

Dramatic results were not obtained by giving menadione parenterally in doses not exceeding 15 mg. for each twenty-four hour period. The number of cases studied and the amount of menadione given were too small to justify clinical conclusions. Since a deficiency of prothrombin is usually present a few hours after the onset of heatstroke, it would be wise to try large doses of menadione, 50 to 60 mg., parenterally when the patient is first seen. Such large doses have been successful in treatment of the untoward effects of dicoumarin (3,3′-methylene-bis-[4-hydroxycoumarin]).

The occurrence of thrombopenia and prothrombin deficiency dictates that early and repeated transfusions of whole blood might be of benefit. Early transfusions were not given in any of the cases herein reported.

Peripheral circulatory failure is not a cause of heatstroke, as evidenced by the fact that the systolic pressure was 130 or more on admission in 6 of our patients. This slight increase in systolic pressure plus the evidence of loss of capillary tone previously referred to suggests that the pooling of blood in dilated vessels may become sufficient to produce circulatory failure. Two patients (cases 6 and 1) did show decided drops in blood pressure soon after their admission, and definite improvement followed infusions of 500 cc. of plasma.

CONCLUSIONS

The hemorrhagic phenomena associated with heatstroke are due to an increase in capillary porosity and a decrease in prothrombin and/or platelets.

The resulting prothrombin deficiency is secondary to hepatic damage.

Large amounts of menadione administered parenterally, early transfusions of whole blood and a regimen to prevent or retard hepatic damage might be of some value in treatment of patients who survive the first few hours.

CHRONIC COR PULMONALE

Sixty Cases Studied at Necropsy

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COR PULMONALE is usually classified into the acute, subacute and chronic types. Acute cor pulmonale is generally caused by massive pulmonary emboli. If over 60 per cent of the vascular bed is occluded in this form, death will result almost immediately. The subacute form, the least frequent of the three, has been accurately described by Greenspan.[1] Secondary endolymphatic carcinomatosis of the lungs is the commonest cause of subacute cor pulmonale. In this condition the metastatic carcinoma diffusely infiltrates the perivascular lymphatics and then secondarily involves the pulmonary arterioles. This involvement interferes with the flow of blood through the pulmonary circuit and results in an increased burden on the right ventricle with eventual failure. The primary site for this type of secondary carcinomatous involvement of the lung is most often in the stomach, but in our experience carcinoma arising in the prostate, liver, kidney, breast or bronchus has also given rise to metastases with similar distribution. Brill and Robertson[2] reported that involvement of the smaller vessels by pulmonary emboli may also result in subacute failure of the right ventricle. Yater and Hansmann[3] have described 2 patients with sickle cell anemia with secondary pulmonary thrombosis in whom subacute cor pulmonale developed. Chronic cor pulmonale, the type with which this report is mainly concerned, results from a much greater variety of anatomic changes. These changes may arise primarily in the bony structures of the chest, in the pulmonary vascular tree or in the lung parenchyma. Those arising as a result of changes in the lung constitute the largest and most important group.

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1. Greenspan, E. B.: Carcinomatous Endarteritis of Pulmonary Vessels Resulting in Failure of Right Ventricle, Arch. Int. Med. **54**:625-644 (Oct.) 1934.

2. Brill, I. C., and Robertson, T. D.: Subacute Cor Pulmonale, Arch. Int. Med. **60**:1043-1057 (Dec.) 1937.

3. Yater, W. M., and Hansmann, G. H.: Sickle Cell Anemia: New Cause of Cor Pulmonale; Report of Two Cases with Numerous Disseminated Occlusions of Small Pulmonary Arteries, Am. J. M. Sc. **191**:474-484 (April) 1936.

CLASSIFICATION

The following classification based on etiology has the additional advantage of grouping the cases according to the clinical behavior of the disease. This classification is not meant to be all-inclusive.

I. Anatomic alterations of the thoracic cage
   A. Kyphoscoliosis
   B. Thoracoplasty
II. Anatomic alterations of the pulmonary vascular system
   A. Main pulmonary arteries
      1. Intrinsic disease of the large pulmonary arteries, such as gummatous or cicatricial pulmonary arteritis (Warthin [4] and Cheney [5])
      2. Pressure on the large pulmonary vessels, such as aneurysm arising from the base of the aorta (Eichler [6] and Delp and Maxwell [7])
   B. Pulmonary arterioles
      1. Primary pulmonary arteriosclerosis; endarteritis obliterans (Ayerza's disease)
      2. Schistosomiasis of pulmonary vessels (Clark and Graef [8] and Shaw and Ghareeb [9])
III. Anatomic alterations of the pulmonary parenchyma
   A. Primary pulmonary emphysema with or without fibrosis
   B. Primary pulmonary disease with secondary emphysema and fibrosis
      1. Pulmonary tuberculosis
      2. Pneumoconiosis
         a. Chronic silicosis
         b. Anthracosis (Ketterer [10] and Helpern [11])
      3. Bronchiectasis
      4. Bronchial asthma
      5. Acute interstitial fibrosis (Hamman and Rich [12])
      6. Multiple cysts of the lung (Willius [13])

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4. Warthin, A. S.: Syphilis of the Pulmonary Artery, Am. J. Syph. **1**:693 (Oct.) 1917.

5. Cheney, G.: Ayerza's Disease: Report of Two Cases, Am. J. M. Sc. **174**:34-45 (July) 1927.

6. Eichler, B.: Personal communication to the authors; to be published.

7. Delp, M. H., and Maxwell, R.: Aneurysm of Aorta with Rupture into Pulmonary Artery, J. A. M. A. **10**:1647-1649 (May 14) 1938.

8. Clark, E., and Graef, I.: Chronic Pulmonary Arteritis in Schistosomiasis Mansoni Associated with Right Ventricular Hypertrophy: Report of a Case, Am. J. Path. **11**:693-706 (July) 1935.

9. Shaw, A. F. B., and Ghareeb, A. A.: The Pathogenesis of Pulmonary Schistosomiasis in Egypt with Special Reference to Ayerza's Disease, J. Path. & Bact. **46**:401-424 (May) 1938.

10. Ketterer, C. H.: Anthracosis and Chronic Pulmonary Heart Disease (Cor Pulmonale), M. Bull. Vet. Admin. **18**:98-100 (July) 1941.

11. Helpern, M.: Personal communication to the authors.

12. Hamman, L., and Rich, A. R.: Acute Diffuse Interstitial Fibrosis of Lungs, Bull. Johns Hopkins Hosp. **74**:177-212 (March) 1944.

13. Willius, F. A.: Cardiac Hypertrophy and Failure Secondary to Diffuse Bilateral Congenital Cystic Disease of Lungs, Proc. Staff Meet., Mayo Clin. **12**: 572-575 (Sept. 8) 1937.

The term "emphysema" as used in this report refers to chronic obstructive emphysema that sometimes goes under the pseudonyms of "hypertrophic emphysema," "large lung emphysema" or "chronic vesicular emphysema." In this condition the lung is in a chronic state of hyperinflation resulting presumably from a diffuse incomplete obstruction of the finer bronchial air passages. On the other hand, it is thought that senile emphysema plays no part whatsoever in the development of cor pulmonale.

SELECTION OF CASE MATERIAL

Cor pulmonale is often a complicating factor of other forms of heart disease, particularly rheumatic heart disease, and occurs most frequently at the age when other forms of heart disease, such as arteriosclerotic and hypertensive forms, are prevalent. In order to present an unequivocal picture of this condition, we have eliminated from our series any case in which the possibility of another significant cardiac factor existed. The cases were selected first on the basis of their anatomic features, and only then was any recourse made to the clinical record. Sixty consecutive cases of cor pulmonale studied at necropsy were selected in which there were no significant evidences either clinical or anatomic, present or preexistent, of hypertension, valvular heart disease, congenital lesions, syphilitic cardiovascular disease or coronary atherosclerosis.

Most of the patients fell into the age group in which coronary atherosclerosis and hypertension are common occurrences. It was, therefore, possible to eliminate only those characterized by moderate to severe coronary arterial changes. Only those cases were selected as examples of cor pulmonale in which the walls of the right ventricle averaged over 5 mm. in thickness and in which the walls of the right ventricle were hypertrophied to a greater degree than those of the left ventricle. Consequently a number of cases of cor pulmonale occurring in pulmonary tuberculosis, in which the heart as a whole may be considerably reduced in size, may have been overlooked.

INCIDENCE AND ETIOLOGY

The fact that these cases are selected renders valueless an attempt to draw any significant conclusion from this series as to the frequency and incidence of this condition. However, in a report by Scott and Garvin [14] there were 50 cases of cor pulmonale described in a series of 6,548 necropsies. Of these 6,548 necropsies, 890 involved cases of cardiac disease. Cor pulmonale, therefore, formed 6.3 per cent of all cases of cardiac disease studied by them at necropsy.

14. Scott, R. W., and Garvin, C. F.: Cor Pulmonale: Observations in Fifty Autopsy Cases, Am. Heart J. **22**:56-63 (July) 1941.

The types and the incidence of the etiologic factors responsible for the development of cor pulmonale in their cases are listed in table 1. In our series there was also a wide variety of etiologic factors (table 2). A cursory comparison will reveal that our observations are in essential agreement with those reported by Scott and Garvin.[14]

TABLE 1.—*Etiologic Factors (Scott and Garvin [14])*

Underlying Pulmonary Conditions	Number of Cases
Emphysema	32
Emphysema and silicosis	7
Emphysema and tuberculosis	5
Emphysema and silicotuberculosis	2
Silicosis	1
Fibrosis	1

TABLE 2.—*Etiologic Factors (Spain and Handler)*

Underlying Pulmonary Conditions	Number of Cases
Emphysema	40
Bronchiectasis	6
Bronchial asthma	6
Silicotuberculosis	3
Pulmonary tuberculosis	2
Kyphoscoliosis	1
Pulmonary arteriolarsclerosis	1
Organized pulmonary thrombi	1

Although not included in this series, there have been observed at Bellevue Hospital such conditions as partial occlusion of the pulmonary artery by an aortic aneurysm, schistosomiasis and anthracosis as causes of cor pulmonale.

AGE, SEX, RACE AND OCCUPATION

Of the 60 patients, 56 were men and 4 were women; 56 were white; 3 were Negroes, and 1 was Chinese. The peak age incidence was between

TABLE 3.—*Distribution by Age*

Age	All Patients	Patients with Emphysema
30 to 40	4	1
41 to 45	3	1
46 to 50	4	2
51 to 55	14	5
56 to 60	12	8
61 to 65	11	10
66 to 70	8	8
71 and over	4	4

50 and 65. For those patients in whom emphysema alone was the apparent etiologic agent, the peak age incidence was definitely higher than for the others (table 3).

Since in both this series and Scott and Garvin's series the number of women was so low, it became of special interest to evaluate the underlying etiologic factors in the conditions of the women. It was found that of the 4 women, in addition to emphysema, 2 had bronchial asthma and 1 had bronchiectasis, while only 1 had chronic emphysema unassociated with other obvious pulmonary disease.

The cause of cor pulmonale in Negroes was also found to follow the same etiologic pattern as in women in that primarily emphysema itself was not the sole underlying factor. Study of the Negroes revealed that emphysema was most likely secondary to other obvious anatomic changes: For example, 1 patient had pulmonary tuberculosis; 1 had bronchial asthma, and in another there were organized and recanalized pulmonary thrombi. This same general pattern was also noted in those patients under the age of 40, among whom, for example, 1 patient had asthma and 2 had bronchiectasis, while only 1 had chronic idiopathic emphysema.

A review of the occupations engaged in by these patients indicated that the majority were employed in hard labor, while only a few performed light or sedentary work. Because Bellevue Hospital serves primarily the low income group, it is not possible to draw any definite conclusions. It is our impression, however, that cor pulmonale is seen more commonly in those engaged in hard laboring occupations. This seems to be particularly true of those patients in whom emphysema alone is the sole underlying pulmonary factor.

Similarly, no definite conclusions can be drawn from the nationality of these patients. While many nationalities were represented, the majority came from the Slavic countries. This, again, is in accord with the findings of Scott and Garvin,[14] who reported that 68 per cent of their patients came from southeastern Europe.

PATHOGENESIS IN THORACIC DEFORMITIES

The 1 patient with kyphoscoliosis in this series was a 55 year old white man with a history of deformity of the chest since childhood. He had complained of a cough productive of mucoid sputum for many years, but it was only several months before his admission to the hospital that he noticed any dyspnea or edema of the ankles. He was admitted to the hospital in a state of congestive heart failure and within a few weeks died. At postmortem examination the myocardium of the right ventricle was seen to be extremely hypertrophied. There was pronounced chronic passive congestion of all the viscera. There was an extreme kyphoscoliosis with the convexity to the right. Emphysema was the only significant abnormal feature in the lungs.

Hertzog and Manz [15] collected 126 cases of heart disease associated with kyphoscoliosis reported in the literature. In the majority of these, the heart was displaced upward and to the opposite side of the scoliosis. The possibility theoretically exists, therefore, that larger pulmonary vessels are kinked by the displacement of the mediastinal structures. It is significant to point out that the constant associated feature in all these cases was the far advanced emphysema of the lung, so that actually it is probable that this is one of the prime factors in the production of the pulmonary hypertension.

Chapman, Dill and Graybiel [16] reported that the average duration of life from the onset of deformity in this type of patient is thirty years. They also noted that the tendency to the development of hypertrophy of the right ventricle was much greater in those patients in whom the scoliosis was to the right. Although constant dyspnea is the most frequent symptom present in this condition, in the case reported by us the dyspnea was an extremely late manifestation. Kyphoscoliosis is responsible for only a small proportion of the cases of cor pulmonale. It was present only once in the 60 cases reported in this series, was not present at all in Scott and Garvin's series [14] and was listed only once in the 38 cases reported by Hallock and Rigler.[17]

Another deformity of the chest which may be associated with cor pulmonale is a long-standing thoracoplasty. Through the courtesy of the medical examiner, we have had the opportunity to observe such a case. The patient was a man 45 years of age, who had had a complete thoracoplasty performed on the right side nine years previously for pulmonary tuberculosis. Detailed clinical studies are not available. However, he did not have any obvious signs of heart failure. The heart weighed 500 Gm. and the myocardium of the right ventricle was over 1 cm. in thickness. The pulmonary arteries and arterioles revealed advanced sclerotic changes. Considerable emphysema was present on the noncollapsed side. Whether the pulmonary hypertension resulted from the deformity of the chest or from the fibrosis and emphysema associated with the tuberculosis could not be determined. Undoubtedly, the question of whether or not long-standing thoracoplasty may result in a strain on the right side of the heart is a subject which deserves further study.

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15. Hertzog, A. J., and Manz, W. R.: Right-Sided Hypertrophy (Cor Pulmonale) Caused by Chest Deformity, Am. Heart J. **25**:399-403 (March) 1943.

16. Chapman, E. M.; Dill, D. B., and Graybiel, A.: The Decrease in Functional Capacity of the Lungs and Heart Resulting from Deformities of the Chest: Pulmonocardiac Failure, Medicine **18**:167-202 (May) 1939.

17. Hallock, P., and Rigler, L. G.: Chronic Cor Pulmonale, Staff Meet. Bull., Hosp. Univ. Minnesota **13**:106, 1941; Am. J. Roentgenol. **50**:453-460 (Oct.) 1943.

PATHOGENESIS IN PULMONARY VASCULAR DISEASE

In an evaluation of the various conditions producing cor pulmonale, it is much easier to explain the pathogenesis of some forms than of others. In primary pulmonary arteriolarsclerosis, pressure on the main pulmonary artery, organized pulmonary vascular thrombi and schistosomiasis of the lungs with pulmonary vascular changes, it is quite obvious that the diminution in the caliber of the blood vessels will lead to an increased resistance to the flow of blood that eventually will result in a strain on the myocardium of the right ventricle. However, in most of the cases, there is no significant primary vascular change that would account for the increased resistance to the flow of blood through the lungs.

In this series there was 1 case that was considered to be an instance of primary pulmonary arteriolarsclerosis. The patient was a 59 year old Russian-born man with a fifteen year history of cardiorespiratory distress. He was never bedridden throughout this period. He went rapidly into a state of congestive heart failure and died within several days. The pulmonary arterioles and arteries had advanced sclerotic changes with pronounced narrowing of the lumens. The heart weighed 475 Gm., and the myocardium of the right ventricle measured 0.9 mm. in thickness. Brill and Krygier [18] reviewed 20 similar cases collected from the literature and pointed out that in order to make this diagnosis on an anatomic basis every other factor that might lead to pulmonary hypertension and then act as a possible cause for the development of secondary pulmonary vascular sclerosis must be eliminated. Although emphysema is present in most of these cases, probably as a secondary nutritional change, the noticeable disproportion between the relatively small degree of emphysema and the extensive pulmonary vascular changes points to the latter as the important factor. The patient in our series was considerably older than the average patient encountered in a case of this type, who is usually 35. In 5 of the 20 cases reviewed by Brill and Krygier,[18] congestive heart failure developed and the patients died relatively rapidly. The same events occurred in our case. In the 20 cases, 50 per cent of the patients were women. This distribution is in contrast to that in cases of cor pulmonale resulting from emphysema, in which only an exceptional case is found involving a woman. The cause of primary pulmonary vascular sclerosis has never been determined. There is no apparent relation between generalized arteriosclerosis and arteriosclerosis in the pulmonary vascular bed. Ayerza's [19] original contention that syphilis is an important factor in

18. Brill, I. C., and Krygier, J. J.: Primary Pulmonary Vascular Sclerosis, Arch. Int. Med. **68**:560-577 (Sept.) 1941.

(Footnotes continued on next page)

the causation of this disease has never been substantiated. He also expressed the belief that the vascular changes were most likely secondary to primary bronchopulmonary disease. This is still an unsettled question.

In our series there was 1 case of cor pulmonale secondary to organized thrombi in the main pulmonary arteries. The patient was a 61 year old Negro man without any significant past history. Four weeks before his admission to the hospital he first noted the gradual onset of dyspnea on exertion. This became rapidly worse, and after an episode of syncope he became intensely dyspneic and died within three days with acute failure of the right side of the heart. The heart weighed 550 Gm.; the wall of the right ventricle averaged 1 cm. in thickness, and there was a large, firmly adherent, organized and partially recanalized thrombus present in the main pulmonary artery. This thrombus extended for a short distance into both the right and the left branches. The lumen of the main pulmonary artery was reduced to approximately one half. There were several smaller fresh thrombi in the smaller pulmonary arteries. The primary site of origin of these thrombi was not determined.

A similar case has been reported by Montgomery,[20] who also observed the extreme rarity of this condition. His patient was a 36 year old woman who died of acute right-sided heart failure after having evidence of such failure in varying degrees for a period of eleven months. Both in our case and in that of Montgomery, the cause for the formation of the thrombus could not be determined. In both cases there were no underlying vascular changes, nor was any site of origin for emboli discovered. In our case, although the clinical history was of short duration, the process undoubtedly had been going on for a long time, as evidenced by the advanced hypertrophy of the myocardium of the right ventricle and the well developed organization and recanalization of the thrombus in the pulmonary artery.

Other cases of the same type have been described by Balboni.[21] It is possible that primary pulmonary vascular sclerosis, described by Brenner,[22] may be the underlying factor in the formation of these thrombi.

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19. Ayerza, L.: Ayerza's Disease: "Black Cardiacs," Rev. Soc. de med. int. **1**:73-83 1925.

20. Montgomery, G. I.: A Case of Pulmonary Artery Thrombosis with Ayerza's Syndrome, J. Path. & Bact. **41**:221-230 (Sept.) 1935.

21. Balboni, V. G.: Multiple Pulmonary Thrombi Associated with Cyanosis and Right-Sided Hypertrophy, New England J. Med. **223**:896-900 (Nov. 28) 1940.

22. Brenner, O.: Sclerosis of Pulmonary Artery with Thrombosis, Lancet **1**:911-914 (April 25) 1931.

Although not included in our consecutive series, a case of pulmonary schistosomiasis at Bellevue Hospital resulting in hypertrophy of the right ventricle has been reported in detail by Clark and Graef.[8] The patient was a 20 year old Puerto Rican youth, who complained of shortness of breath and swelling of the legs for one month prior to admission to Bellevue Hospital. His chief complaint on his admission was pain in the chest of three days' duration. Although rapidly digitalized, he became increasingly dyspneic and died twenty hours after his admission. The heart weighed 360 Gm., while the right ventricle measured 8 mm. in thickness and the left ventricle 10 mm. A chronic pulmonary arteritis had been produced by infection with Schistosoma mansoni. In the liver there was a nodular cirrhosis characteristically associated with this parasite. Shaw and Ghareeb,[9] in a review of 282 necropsies performed on patients with schistosomiasis, reported that in 33 per cent there was evidence of pulmonary infection and that 2 per cent of all patients died as a result of the ensuing right-sided heart failure. They described the pathologic picture in the lungs as beginning with an acute necroting arteriolitis that resulted from the action of the schistosome ova on the intima and media of the pulmonary arterioles. This was soon followed by an obliterative arteriolitis that later became recanalized. The new vessels became dilated, with resultant angiomatoid formation. This vascular change resulted in the obstruction to the flow of blood through the lungs.

Recently we have seen a case of syphilitic cardiovascular disease in which there was an aneurysm at the base of the aorta that compressed the pulmonary artery and resulted in hypertrophy of the right ventricle. This case, to be published in detail by Eichler,[6] was that of a 42 year old white man admitted to the hospital with signs of right-sided heart failure, who died shortly after his admission. Scott and Garvin [14] mentioned a similar case. In rare instances the aortic aneurysm, in addition to pressing on the pulmonary artery, may rupture directly into it (Delp and Maxwell [7]).

PATHOGENESIS IN PRIMARY DIFFUSE OBSTRUCTIVE EMPHYSEMA

In 40 of the 60 cases, pulmonary emphysema was considered to be the sole underlying pulmonary condition responsible for the development of the hypertrophy of the right ventricle. It has already been noted that among these cases only 1 of the patients is a woman and that the age incidence is higher than for the other types. These observations merely reflect the fact that advanced emphysema with considerable increase of the anteroposterior diameter of the chest is uncommon in women while it is of frequent occurrence in men past middle age. Furthermore, men in this age group are more often engaged in heavy manual labor than are women. For many years it

was thought that there was no direct relation between the pulmonary emphysema and the cardiac failure that was so often present in these cases. But in recent years it has been generally accepted that a close relation exists. There still remains, however, considerable speculation as to the exact mechanism whereby pulmonary emphysema produces hypertrophy of the myocardium of the right ventricle. Among the factors suggested have been pulmonary vascular sclerosis, diffuse fibrosis of the lungs, anatomic obliteration of some of the pulmonary vascular bed, the existence of vascular shunts between the systemic and pulmonary circulations, overfilling of the heart in emphysema, inspiratory pull on the pericardium and polycythemia.

The pulmonary arteriolarsclerosis that is found in some of these cases is generally considered to be a secondary change. It is often absent and when present is too insignificant in degree to be responsible for the primary increase of pulmonary vascular resistance (table 4). Parker,[23] in studying 32 cases of emphysema, found that pulmonary vascular changes were present in 80 per cent of the cases but concluded that there was no causal relation between this change and the hypertrophy of the right ventricle that was present in 72 per cent of his cases. In our series, pulmonary vascular sclerosis was present in 20 of 40 cases of emphysema and in only a few of these to a moderate or advanced degree (table 4).

Pulmonary fibrosis often accompanies emphysema of the lungs. However, like pulmonary arteriolarsclerosis, pulmonary fibrosis is not constantly present. It was present in only 16 out of the 40 cases of emphysema (table 4).

In order for the fibrosis to produce an increased resistance to the flow of blood through the lungs, it must of necessity be a diffuse and fine fibrosis that encircles the smaller blood vessels. The fibrosis following such conditions as silicosis and pulmonary tuberculosis is often a nodular, dense, localized fibrosis. Furthermore, in such a condition as tuberculosis, in which there is extensive destruction of pulmonary tissue, it has been demonstrated that the circulation to the diseased and fibrotic area is to a great extent taken over by the collateral capillaries coming from the bronchial arterial system, so that any effect of the fibrosis in these particular areas on the circulation does manifest itself in the systemic rather than in the pulmonary circuit. In the conditions in which diffuse and fine fibrosis do occur, as in acute diffuse interstitial fibrosis of the lungs, recently reported by Hamman and Rich,[12] and in acute silicosis resulting from exposure in talc and abrasive soap

23. Parker, R. L.: Pulmonary Emphysema: Relation to Heart and Pulmonary Arterial System, Ann. Int. Med. **14**:795-809 (Nov.) 1940.

industries, reported by Chapman,[24] there is not only arterial obstruction but also diffuse involvement of the smaller bronchioles resulting in obstructive emphysema. It is possible, therefore, that the pulmonary hypertension in part at least may be mediated through this mechanism. It has become a clinical habit when the diagnosis of emphysema is made to assume that fibrosis is always present—thus, the clinical usage of the term "fibrosis and emphysema of the lungs." This, however, is

TABLE 4.—*Relation Between the Weight of the Heart, Hypertrophy of the Right Ventricle, Degree of Emphysema, Pulmonary Arteriolarsclerosis, Diffuse Fibrosis of the Lungs and Bronchitis.*

Age	Sex	Weight of Heart, Gm.	Width of Right Ventricle, Cm.	Obstructive Emphysema	Pulmonary Arteriolar-sclerosis	Diffuse Fibrosis of Lungs	Bronchitis
62	M	350	0.6	3+	0	0	0
68	M	350	0.6	3+	0	0	1+
55	M	350	0.65	3+	0	0	2+
62	M	350	0.6	2+	0	0	0
71	M	380	0.7	3+	0	0	1+
55	M	390	0.9	4+	1+	1+	1+
70	M	390	0.7	4+	1+	0	1+
47	M	400	0.65	3+	0	0	0
70	M	400	0.8	4+	1+	1+	1+
64	M	400	0.7	3+	0	0	1+
57	M	400	0.6	3+	0	0	1+
67	M	400	0.7	3+	2+	1+	0
42	M	400	0.75	4+	1+	0	1+
55	M	400	0.6	4+	0	0	0
65	M	400	0.8	3+	0	2+	2+
80	M	400	0.8	3+	0	0	0
37	M	400	1.0	3+	1+	0	1+
88	M	400	0.8	3+	0	0	0
67	M	400	1.0	4+	0	0	1+
68	M	400	0.7	3+	0	1+	0
53	F	410	0.9	3+	0	1+	1+
54	M	410	0.8	3+	1+	0	1+
52	M	420	0.8	3+	1+	1+	0
67	M	420	0.8	4+	2+	2+	1+
61	M	420	0.8	4+	0	0	2+
45	M	440	0.6	4+	0	1+	2+
54	M	450	0.7	2+	1+	1+	0
69	M	450	1.3	3+	1+	0	1+
53	M	450	1.0	4+	0	0	1+
59	M	450	0.85	3+	1+	1+	1+
60	M	470	0.65	3+	0	1+	0
62	M	500	0.6	3+	0	0	2+
46	M	500	0.8	3+	1+	0	1+
55	M	520	1.0	3+	1+	0	0
57	M	540	1.1	4+	1+	0	2+
62	M	550	1.0	3+	3+	2+	0
64	M	570	0.9	4+	1+	0	0
60	M	600	1.0	3+	1+	1+	1+
68	M	770	1.4	3+	2+	0	0

not correct, since in many cases of emphysema there is practically no fibrosis present.

Anatomic obliteration of the pulmonary vascular bed as a result of pulmonary emphysema or other forms of pulmonary disease has also been offered as an explanation for the developing pulmonary hypertension. This, undoubtedly, is an important factor in increasing the

24. Chapman, E. M.: Acute Silicosis, J. A. M. A. **98**:1439-1441 (April 23) 1932.

resistance to the flow of blood through the lungs. However, it is necessary to obliterate almost 80 per cent of the pulmonary vascular bed in dogs before any changes occur in the right ventricle (Lichtheim[25]). Furthermore, in these animals the remaining pulmonary tissue necessarily becomes emphysematous, so that the vascular bed is still further reduced. It must be pointed out that this experimental condition in animals is not applicable to human beings in that human beings often continue at hard laboring work over a period of years while the obliteration of the pulmonary vascular bed develops. Also, the resulting emphysema in the animals is not truly an obstructive emphysema but is one in which the lung expands to compensate for the increased space in the chest cavity. This experiment is somewhat analagous to the condition in a patient who has undergone a pneumonectomy, whose remaining lung becomes emphysematous in order to fill in the residual space. In addition, this type of patient would no longer engage in hard labor and would most likely be bedridden or lead a sedentary life. There are no studies available as to whether or not hypertrophy of the right ventricle developed in these patients. To what extent anatomic obliteration of the pulmonary vascular bed results in increased resistance to flow is not clear, because undoubtedly some readjustment of the circulation must take place whereby the volume of blood going through the affected lung or lungs is somewhat decreased, probably through vascular shunts, a greater amount of blood going to uninvolved portions, or else through a general readjustment between the systemic and pulmonary circulations.

Wood and Miller,[26] in a report of a series of injections of dye performed during studies of the relationship between the bronchial and pulmonary arterial circulations, mentioned the possibility of increased communications in the form of large vascular shunts between the two circulatory systems in pulmonary disease. These, they claimed, might allow a higher systemic pressure from the bronchial circulation to manifest itself in the pulmonary circuit with a subsequent strain on the right side of the heart, acting in the same manner as an arteriovenous fistula. These increased communications or shunts have not as yet been demonstrated in primary obstructive emphysema.

Compensatory polycythemia that occurs not infrequently in obstructive emphysema acts most likely only as a secondary aggravating factor in the development of pulmonary hypertension. About 80 per cent

25. Lichtheim, cited by Rehfisch: Zur Aetiologie der Vergrösserung der rechten Herzkammer, insbesondere bei behindeter Nasenatmung, Deutsche med. Wchnschr. **44**:227, 1918.

26. Wood, D. A., and Miller, M.: Role of Dual Pulmonary Circulation in Various Pathologic Conditions of Lungs, J. Thoracic Surg. **7**:649-670 (Aug.) 1938.

of the patients with emphysema have evidence of pulmonary hypertension in the form of pulmonary vascular sclerosis (Parker [23]). About 40 per cent of the patients with pulmonary tuberculosis also manifest some evidence of pulmonary hypertension in the form of hypertrophy of the right ventricle (Higgins [27]). Yet, polycythemia is surely not present in the same degree of frequency either in emphysema or in pulmonary tuberculosis. Zadek [28] pointed out that the severest grades of polycythemia vera may be encountered without any evidence of cardiovascular change. Fishberg [29] stated that the absence of high blood pressure in many cases of polycythemia vera shows that the augmented viscosity has had little effect on blood flow. He offered the explanation that the axial flow of red blood corpuscles in small vessels allows for only a layer of plasma to come into contact with the vessel wall, so that an increase in the number of red blood cells would not necessarily increase the resistance to the flow of blood. It is also of interest that Hess [30] could produce no cardiac hypertrophy by experimentally induced plethora, while Peacock [31] cited experiments which tended to show that increases of volume and of viscosity of the blood do not increase the blood pressure.

Kountz, Pearson and Koenig [32] found normal circulation times in dogs in which emphysema had been produced. They concluded from this fact that there was no increased resistance to the flow of blood through the lungs in emphysema. This conclusion appears to be unwarranted, because the circulation time does not necessarily reflect the degree of increased pulmonary vascular resistance but reflects rather the degree of heart failure. In systemic hypertension, in which there is often obvious increased peripheral vascular resistance, the circulation time is usually increased only when the heart begins to fail. The same is undoubtedly true of pulmonary hypertension and right-sided heart failure.

The explanation offered by Kountz, Alexander and Prinzmetal [33] that the hypertrophy of the heart occurs mainly in early stages of

27. Higgins, G. K.: The Effect of Pulmonary Tuberculosis upon the Weight of the Heart, Am. Rev. Tuberc. **49**:255-275 (March) 1944.

28. Zadek, I.: Die Polycythämien, Ergebn. d. ges. Med. **10**:355-400, 1927.

29. Fishberg, A. M.: Heart Failure, ed 4, Philadelphia, Lea & Febiger, 1940, p. 357.

30. Hess, L., and Saxl, P., cited by Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, p. 2392.

31. Peacock, H. A.: Blood Pressure and Blood Volume in Cases of Polycythemia Vera, Proc. Staff Meet., Mayo Clin. **4**:286-288 (Sept. 25) 1929.

32. Kountz, W. B.; Pearson, E. F., and Koenig, K. F.: Observations on Intrapleural Pressure and Its Influence on the Relative Circulation Rate in Emphysema, J. Clin. Investigation **11**:1281-1291 (Nov.) 1932.

(Footnotes continued on next page)

emphysema owing to a decreased negative intrapleural pressure with subsequent overloading of the heart is not supported by the clinical course in these cases. Cor pulmonale occurs not in the early stages but in the late and advanced stages of emphysema. Furthermore, once the diaphragm becomes fixed in its lowered position this overloading mechanism no longer operates, and one would naturally expect some alleviation, or at least a slower development, of the right-sided failure late in the disease. This again does not correspond with the usual clinical experience.

It appears more likely that there is an increased resistance to the flow of blood through the lungs in cases of advanced emphysema that over a period of time exerts a strain on the right side of the heart. There is much evidence to support this view. In the 40 cases in this series, primary obstructive emphysema was the only single constant feature, while, as has been mentioned before, the fibrotic and vascular changes were not present in every case, and when they were present it was usually in the more advanced stages, indicating that these were secondary rather than primary changes (table 4).

The lung in emphysema is in a constant state of overdistention. This is obvious at the time of postmortem examination, and often the lungs are found not only to fill the chest cavity completely but to bulge past the midline over the precordium. Furthermore, in pressure studies on large emphysematous bullae positive pressures are often encountered. Intrapleural pressure readings taken during the expiration on patients with emphysema usually range from -1 or -2 to $+2$. These values tend to indicate that at least during the expiratory phase of the respiratory cycle there is an increased pressure above the normal within the lungs. Intrabronchial pressure studies taken at the same time reveal that this increased pressure is not reflected within the bronchial tree, since the readings taken were normal (Neergard and Wirz [34]). This, therefore, points to the site of increased pressure as being intra-alveolar rather than intrabronchial. It has also been demonstrated that increased intra-alveolar pressure exerts a direct effect on elevating pressure of the pulmonary vascular circuit. This was demonstrated by Maier [35] during the course of an intrathoracic surgical procedure. The patient in question was receiving anesthesia under positive pressure through a closed circuit. Pressure in this anesthesia circuit was deliberately raised. At the same time pressure recordings

33. Kountz, W. B.; Alexander, H. L., and Prinzmetal, M.: The Heart in Emphysema, Am. Heart J. **11**:163-172 (Feb.) 1936.

34. Neergard, K., and Wirz, K.: Die Messung der Strömungswiderstände in den Atemwegen des Menschen in besondere bei Asthma und Emphysem, Ztschr. f. klin. Med. **105**:51-82, 1927.

35. Maier, H.: Personal communication to the authors.

were made of the pulmonary vascular circuit. It was noted that there was a direct relation between the pressure of the anesthesia circuit and the degree of elevation of the pressure of the pulmonary vascular system. The overdistended lung in emphysema, in which there is an increased alveolar pressure at least during the expiratory phase of the respiratory cycle, is within an enclosed and relatively fixed space, the thoracic cage. Thus, when this lung expands and exerts its increased pressure, it must do so at the expense of the compressible structures within the lung and chest. In turn, one notes that the diaphragm is pushed down; the rib spaces become widened; the anteroposterior diameter of the chest is increased, and the pulmonary parenchyma overlaps the precordium. The capillaries and smaller blood vessels within the lung are also compressible structures. It therefore seems reasonable that this increased pressure in the alveoli in cases of emphysema will also exert its pressure effects on the smaller blood vessels and capillaries coursing through the interalveolar septums. These pressure effects will increase the resistance to the flow of blood through these vessels, and, in turn, this increased resistance means more work for the myocardium of the right ventricle in order to maintain the normal cardiac output per beat. Eventually the burden will become so great that the right ventricle will become hypertrophied and may fail. This resistance to the flow of blood with the subsequent hypertrophy of the right side of the heart is therefore not necessarily based solely on the anatomic obliteration of the pulmonary vascular bed, as has been previously postulated, but, in addition, it is a functional pressure resistance relation occurring in functioning pulmonary tissue as exerted over a long period. Striking proof of this assumption is in the fact that cor pulmonale is infrequent in the advanced bullous forms of emphysema, in which there is pronounced anatomic obliteration of the blood vessels, while, on the other hand, it is relatively common in the finer diffuse forms of emphysema. Such associated phenomena as polycythemia that increases the viscosity of the blood, pulmonary arteriolarsclerosis, fibrosis impinging on the vessels, possible bronchopulmonary arterial shunts and overloading of the heart probably all play secondary and aggravating roles.

The question arises as to why cor pulmonale will develop in some cases of emphysema while in others it will not. The answer does not seem to be in any single factor, although Eppinger [36] tried to find one many years ago. He grouped the cases of obstructive emphysema into two types: those in which there was a primary bronchitis, in which cor pulmonale did not develop, and those in which there was no primary

36. Eppinger, H.: Das Emphysem der Lungen, Vrtljschr. f. d. prakt. Heilk. **4**:1-80, 1876.

bronchitis, in which cor pulmonale did develop. He stated that the collateral circulation between the pulmonary and the arterial systems that developed in those cases in which there was a primary bronchitis prevented any increased circulatory strain on the myocardium of the right ventricle. However, in our series there were a number of cases in which bronchitis had been present for at least thirty years (table 4). It would be difficult to say in these cases whether the bronchitis was primary or secondary, but at any rate it was present for a sufficiently long period that a collateral circulation could have developed. Nevertheless, cor pulmonale did develop in these cases. Similarly, according to Eppinger,[36] cor pulmonale should not have been present in those cases in which the emphysema was secondary to bronchiectasis, since there was sufficient collateral circulation developing over a period of time as a result of the underlying infection and the proliferation of granulation tissue. Here again, cor pulmonale was found. Furthermore, if such collateral circulation should develop to relieve the pressure, one would expect to see numerous dilated veins or venules in the region of the bronchi and bronchioles. These have not been observed. The answer as to why cor pulmonale develops in certain cases of emphysema and does not in others seems to lie in the interplay of many factors, such as the duration, severity and diffuseness of the emphysema, the age at the time of onset, the constitution of the patient, the absence or presence of infection and, most important of all, the type of present and past occupations. The proper combination of some or all of these factors in any person will result in a strain on the myocardium of the right ventricle. Parker[23] reported that in 72 per cent of the 32 cases of emphysema there was revealed evidence of hypertrophy of the right ventricle. Potentially, hypertrophy of the right ventricle can develop in any case of primary obstructive emphysema if the proper combination of factors is present.

PATHOGENESIS IN PULMONARY TUBERCULOSIS

The 2 patients with pulmonary tuberculosis associated with cor pulmonale were men, aged 63 and 39. Both revealed advanced pulmonary tuberculosis with widespread dissemination throughout both lungs, diffuse fibrosis and bilateral chronic obliterative pleuritis. Advanced emphysema was present, and there had been signs and symptoms of right-sided heart failure. The incidence of hypertrophy of the right ventricle in pulmonary tuberculosis varies in different reports from 4.6 per cent or even lower to as high as 40 per cent. This difference may be due to the variations in the postmortem methods of examination of the heart. When the gross measurement of the right ventricle is recorded without taking into account the general decrease of the size of the heart in tuberculosis, the incidence is usually found

to be low. On the other hand, if the technic of Herrmann [37] is employed, in which the right side of the heart is dissected away from the left side and the relative degree of hypertrophy of the two ventricles is taken into consideration, the incidence is much higher. This method was utilized by Higgins [27] in a recent study of the weight of the heart in tuberculosis. He also took into account the general decrease of the size of the heart as a result of the malnutrition and emaciation coincident with tuberculosis. In his study the incidence of hypertrophy of the right ventricle in association with pulmonary tuberculosis was reported as 40 per cent. Roberts and Lisa,[38] however, stated that the only reliable method for determining hypertrophy of the right ventricle is by histologic examination, and they found an incidence of 3 per cent.

Ackerman and Kasuga [39] found no definite correlation between the type and complications of tuberculosis and the incidence and degree of hypertrophy of the right ventricle, with the one exception that hypertrophy of the right ventricle was directly related to the duration of the tuberculosis. Such factors as obliteration of the pleural space, spontaneous or produced pneumothorax, far advanced pulmonary destruction, adhesions and kinking of the great vessels have all been suggested as possible underlying factors. Higgins [27] stated that none of these factors has a causal relation to development of cor pulmonale in pulmonary tuberculosis. He stated the opinion that the secondary emphysema resulting from fibrosis is the most likely etiologic factor.

In the 2 cases reviewed in our series all the aforementioned potential factors, with the exception of far advanced pulmonary destruction, were present. It was, therefore, impossible to draw any specific conclusions except that advanced destruction of the lung is apparently not necessary for the development of this process. Emphysema was advanced in both cases and may very well have been the important factor in the development of the hypertrophy of the right ventricle.

PATHOGENESIS IN BRONCHIAL ASTHMA

There were 6 cases of bronchial asthma in this series. Each of the patients had extensive diffuse emphysema. In these cases of bronchial asthma in which cor pulmonale developed it probably did so on the basis of associated emphysema. In bronchial asthma the presence

37. Herrmann, G. R.: Experimental Heart Disease: Methods of Dividing Hearts with Sectional and Proportional Weights and Ratios for Two Hundred Normal Dogs' Hearts, Am. Heart J. **1**:213-231 (Dec.) 1925.

38. Roberts, J. E., and Lisa, J. R.: Heart in Pulmonary Tuberculosis: Clinico-Pathological Study of One Hundred Autopsied Patients, Am. Rev. Tuberc. **47**: 253-262 (March) 1943.

39. Ackerman, L. V., and Kasuga, K.: Chronic Cor Pulmonale: Its Relation to Pulmonary Tuberculosis, Am. Rev. Tuberc. **43**:11-30 (Jan.) 1941.

of an increased intra-alveolar pressure, at least for temporary periods during outright asthmatic attacks, is much more obviously recognized than a constant expiratory increase of intra-alveolar pressure with long-standing emphysema. In the final analysis, however, the mechanism appears to be the same. Schiller, Colmes and Davis [40] analyzed a series of 15 cases of bronchial asthma studied at necropsy and found 5 in which there was a definite degree of hypertrophy of the right ventricle. Huber and Koessler [41] reported 2 cases of hypertrophy of the right ventricle in a series of 5 cases of bronchial asthma studied at necropsy. Both groups of observers noted that there was a direct relation among the duration, frequency and length of attacks of asthma, the degree of emphysema and the degree of hypertrophy of the right ventricle.

PATHOGENESIS IN SILICOSIS AND BRONCHIECTASIS

There were 6 cases of bronchiectasis and 3 of silicosis. In both of these conditions there were found both a focal and a diffuse fibrosis within the lungs. Nodular or focal fibrosis appears to be unrelated to the development of the emphysema. The fine fibrosis that surrounds the smaller bronchi often produces an extreme emphysema of the obstructive type. It is interesting to note that, particularly in cases of silicosis, the development of cor pulmonale is not parallel necessarily to the degree of massive nodular fibrosis. It is rather more closely associated with the more diffuse, finer fibrosis. This association is obvious in such forms of silicosis as the acute forms developing after exposure to talc and asbestosis, in which the fibrosis tends to follow the bronchial tree and blood vessels rather than to occur in the nodular form. Therefore, most likely, in those cases of silicosis and bronchiectasis in which cor pulmonale develops it does so on the basis of the secondary emphysema that so often reaches an advanced state in these conditions. This assumption is probably also true of any other pulmonary disease in which a diffuse fine fibrosis results.

SUMMARY OF MORPHOLOGIC OBSERVATIONS

The salient morphologic changes were noted in the 60 cases studied at necropsy. The average weight of the heart was 460 Gm., with the smallest heart weighing 350 Gm. and the largest 770 Gm. The average thickness of the wall of the right ventricle was 0.8 cm., with the extremes of 0.6 and 1.4 cm. Although the dominant observation was

40. Schiller, I. W.; Colmes, A., and Davis, D.: The Occurrence of Cor Pulmonale in Cases of Bronchial Asthma, New England J. Med. **228**:113-117 (Jan. 28) 1943.

41. Huber, H. L., and Koessler, K. K.: The Pathology of Bronchial Asthma, Arch. Int. Med. **30**:688-760 (Dec.) 1922.

the hypertrophy of the right ventricle, the left ventricle in a number of instances was hypertrophied from a minimal to a moderate degree. Hypertrophy of the left ventricle in cor pulmonale may be explained on the basis of anoxemia. Smith and Bartels [42] produced cardiac hypertrophy in dogs by ligating the coronary arteries. Further evidence that impaired nutrition of the myocardium can lead to hypertrophy was present in a most unusual case described by Bland, White and Garland,[43] in which there was an anomalous origin of the coronary arteries from the pulmonary artery. It is known that the inhabitants of the mountain regions of Peru, where there is a lower concentration of oxygen in the atmosphere, consistently revealed generalized enlargement of the heart. Vacek [44] subjected a series of mice to an atmosphere in which there was a lowered oxygen content and also found consistent enlargement of the heart. Thus, it seems possible that the hypertrophy of the left ventricle can result from severe anoxemia that is so often present in emphysema. This may also account to a certain extent for some of the hypertrophy of the right ventricle.

Mural thrombi in the right atrial appendage were present in 6 instances; none was noted in the left atrium. Thrombi were found in the smaller branches of the pulmonary arteries in 5 instances. Whether or not these were embolic or stasis thrombi was not determined. In 6 cases the tricuspid ring was noticeably dilated.

The liver and spleen were constantly the site of varying degrees of chronic passive congestion. In 3 of the cases there was cardiac cirrhosis. Thus, there was an incidence of cardiac cirrhosis of 5 per cent, whereas in chronic passive congestion of the liver associated with all forms of heart failure the incidence is usually lower (Boland and Willius [45]). The cases of cor pulmonale associated with cardiac cirrhosis were of long duration with several episodes of decompensation. Varying degrees of ascites were commonly observed. In only 3 cases was a right-sided pleural effusion demonstrated at the time of necropsy.

The other significant changes were related to the underlying pulmonary disease. In the cases of emphysema these changes consisted of varying degrees of fibrosis, pulmonary arteriolarsclerosis and chronic

42. Smith, H. L., and Bartels, E. C.: Gross Cardiac Hypertrophy in Myocardial Infarction, Am. J. M. Sc. **184**:452-455 (Oct.) 1932.

43. Bland, E. F.; White, P. D., and Garland, J.: Congenital Anomalies of Coronary Arteries, Am. Heart J. **8**:787-801 (Aug.) 1933.

44. Vacek, T.: Functional Adaptation of the Heart in Mice Living Under Insufficient Oxygen Supply, Arch. f. d. ges. Physiol. **212**:357-364, 1926.

45. Boland, E. W., and Willius, F. A.: Changes in Liver Produced by Chronic Passive Congestion with Special Reference to the Problem of Cardiac Cirrhosis, Arch. Int. Med. **62**:723-739 (Nov.) 1938.

bronchitis, in addition to the far advanced emphysema. The other underlying pulmonary conditions, such as bronchiectasis, silicosis and tuberculosis, were present in the incidence indicated in table 1.

The relation between chronic bronchitis and emphysema was of special interest. In the 40 cases of diffuse obstructive emphysema, there was some anatomic evidence of inflammatory change in the bronchial tree in 75 per cent of the cases. Whether or not this close relation points to bronchitis as a possible factor in the development of the emphysema or whether bronchitis is purely a secondary phenomenon occurring in a lung with lowered resistance cannot be answered at the present time. In relation to this close association of bronchitis and emphysema, it was noted clinically that in a majority of these cases a cough productive of a white mucoid sputum was an early and constant occurrence.

Since cases of obvious coronary atherosclerosis were excluded from this study, the fact that there was only a minimal occurrence of atherosclerosis despite the fact that the cases represented an older age group is of no significance whatsoever. The degree of aortic atherosclerosis was typical of the age group studied and bore no relation to the degree of pulmonary vascular sclerosis.

CLINICAL PICTURE

Brill,[46] in analyzing the clinical picture of cor pulmonale, divided the clinical course into two phases: the early pulmonary phase, in which the signs and symptoms of the underlying pulmonary disease predominate, and the later cardiac phase, in which the signs and symptoms of failure of the right ventricle are manifest. In the first phase, one usually finds the dyspnea, hemoptysis, cyanosis, polycythemia and clubbing of the fingers, which are dependent on pulmonary insufficiency, in addition to the more or less specific signs and symptoms of the primary pulmonary lesion; while in the second phase, the engorged veins of the neck, enlarged liver, generalized edema, increased venous pressure and slowed circulation time are the obvious observations.

The transition from one phase to the other is often undetected, since the dyspnea and cyanosis, the early symptoms of cardiac failure, are also the symptoms manifested by the underlying pulmonary disease. Whereas in most forms of heart failure the onset of a break in myocardial reserve is heralded by the appearance of dyspnea, patients with cor pulmonale usually have been dyspneic and cyanotic for many years as a result of pulmonary insufficiency. However, an increase in these symptoms or the appearance of orthopnea in a person who previously

46. Brill, I. C.: The Clinical Manifestations of the Various Types of Right-Sided Heart Failure (Cor Pulmonale), Ann. Int. Med. **13**:513-522 (Sept.) 1939.

could lie flat may be indicative of a break in compensation. Similarly, an intensification of the cyanosis already present far out of proportion to the dyspnea is of great significance in the detection of an early break in myocardial reserve. Cyanosis is more intense in patients with cor pulmonale with cardiac failure than in those with any other form of heart disease; hence, the term "black cardiacs."

In most of the cases reported in this series, the presenting complaint on the patient's admission to the hospital was an increase in the shortness of breath that had been present in a milder degree for many years. In a few, the presenting complaint for which the patient sought admission was swelling of the ankles. Seven patients had a chief initial complaint of precordial pain; in 1 of these the pain was associated with syncope. Of these 7 patients, 1 had burning pain over the left pectoral region for a period of four days prior to his admission. This was associated with dyspnea. Another complained of pain in the chest for several months, also associated with intense dyspnea. The remaining 5 patients had precordial pain, the duration of which ranged from ten to fourteen days. In 2 of these, however, the pain seemed to be of pleuritic rather than of cardiac origin. In examination of none of these patients with precordial pain was any electrocardiographic evidence of coronary occlusion with myocardial damage demonstrated, nor did postmortem examination reveal any significant degree of coronary sclerosis or myocardial fibrosis. The intense cyanosis raises the question whether myocardial anoxemia might have been responsible for the pain.

While in most cases the onset of cardiac failure was insidious, in a fair number there were manifested more or less acute episodes of cardiac failure. The precipitating factors in these cases were intercurrent infections of the respiratory tract, attacks of asthma and, in 1 case, a carbuncle of the neck. The patients usually complained of rapidly increasing dyspnea. Some complained of pain in the epigastrium, in 1 case so severe and associated with such an acute tenderness of the liver that the diagnosis on admission was acute cholecystitis. A few complained of syncope, while 2 patients were brought in to the hospital in coma.

In the cases of severe acute cor pulmonale, the most striking features on physical examination are the intense "black cyanosis," chiefly of the lips and also of the nail beds and skin; the prominent eyes, giving rise to the term "froglike" in our service; the suffused and watery condition of the conjunctivas, resulting from the intense chemosis; the purplish tongue, usually also dry as a result of continued mouth breathing, and the usually full and prominent veins of the neck, in which pulsation is rare. In obese patients whose veins of the neck are deep seated, this feature may not be noted.

In most of our cases emphysema was the underlying pulmonary condition, and in these there was a disproportionate increase in the anteroposterior diameter of the chest over the transverse diameter. The physical signs in the lung were dependent on the morphologic changes present. In none of the cases was a pleural effusion detected clinically. The cardiac borders were difficult to detect by percussion, so that in most of these cardiac enlargement could not be determined on physical examination. Similarly, a point of maximum impulse was frequently absent or was displaced to the epigastrium, where the pulsations of the inferior surface of an enlarged right ventricle could be palpated.

The cardiac sounds were usually distant when emphysema was present. In the vast majority the second pulmonic sound was accentuated. In 7 cases, however, the aortic second sound was greater than the pulmonic. In one third of the cases systolic apical murmurs were heard, to which no clinical significance was attributed. In 2 cases transient systolic and diastolic murmurs were heard over the pulmonic area by various observers, so that in 1 of these the diagnosis of congenital heart disease was entertained. Whether these were caused by functional pulmonary arterial dilatation or were the result of increased tension within the pulmonary circuit could not be definitely ascertained. Auricular fibrillation was present in only 9 instances. The blood pressures ranged from 100 to 160 systolic and from 60 to 100 diastolic. As has been previously stated, the cases in which higher pressures were encountered were deliberately eliminated.

The liver was palpably enlarged in most of the cases, and in those in which the cardiac failure was rapid it was frequently tender. Ascites was noted in those cases of chronic failure. Edema of the ankles was present to varying degrees, depending on the degree and duration of cardiac failure. Clubbed fingers were definitely present in 19 of the 60 cases, while in a smaller number early changes, such as downward curvature of the finger nails, were observed.

LABORATORY OBSERVATIONS

Laboratory data available on the clinical material studied revealed no single consistent diagnostic test. The most significant changes appeared in the erythrocyte count. Polycythemia was present in 14 of the 39 cases in which blood counts were made. The extremes ranged from 3,300,000 to 6,500,000, with an average of 4,960,000. These values must be considered in the light of the following limitations. The determinations were performed over a period of years by various persons, giving rise to a considerable margin of error as a result of individual variation in technic. In addition, most of our patients come from the low income districts, and the effect of nutritional

inadequacy must play a part. Weber,[47] in a study of secondary polycythemia, reported counts as high as 10,000,000. In our own experience, in a few cases of cor pulmonale not reported in this series, we have seen similar high counts. There appeared to be no correlation between the onset or degree of failure and the degree of polycythemia. While polycythemia frequently accompanies cor pulmonale, it need not necessarily be present in order for the diagnosis to be made.

Such tests as studies of circulation time and recordings of venous pressure were not performed as a routine. The circulation times, whenever studied, were elevated and correlated well with the degree of failure. Kountz and Alexander [48] recorded that the venous pressure was consistently elevated in emphysema alone. In our experience, the determination of venous pressures in these cases proved of questionable value. For many patients with extreme degrees of failure of the right ventricle whose circulation times were increased, the recordings of venous pressure were normal or even lower. The chief difficulty arises from the fact that it is hard to establish an accurate base line at the level of the auricle in patients with extreme emphysema.

Roentgenographic studies of the chest revealed the expected and typical changes in the pulmonary parenchyma associated with the underlying pathologic pulmonary condition. The cardiac silhouette, on the other hand, showed great variations. In a relatively small number, the cardiac shadow showed definite evidence of enlargement and alterations in the cardiac borders consistent with an enlarged right ventricle. In these cases the left cardiac border showed either straightening or prominent convexity in the area of the pulmonary artery in the posteroanterior view, and fluoroscopic examination revealed the associated displacement of the point of opposite impulse delineating right from left ventricle thrusts in an apical direction. These classic roentgenographic findings in cor pulmonale were seen in those cases in which the underlying pulmonary change was at a minimum as compared with the interference with the pulmonary circulation, that is, in the case of primary pulmonary arteriolarsclerosis and in the cases of pulmonary fibrosis with relatively little pulmonary emphysema.

However, in the great majority of cases in this series, the classic roentgenographic picture of cor pulmonale was masked or hidden by the alterations in the chest created by extensive emphysema, fibrosis, pleural obliteration or kyphoscoliosis. In the cases of emphysema, the depression of the diaphragm resulted in an elongation of the mediastinum, so that the heart appeared smaller than normal and the normal

47. Weber, F. P.: Secondary Forms of Polycythemia Rubra—Ayerza's Disease, Brit. M. J. **2**:658-660 (Oct. 30) 1920.

48. Kountz, W. B., and Alexander, H. L.: Emphysema, Medicine **13**:251-316 (Sept.) 1934.

cardiac contours were obliterated. The increase in lateral diameter of the chest resulting from the elevation of the thoracic cage associated with emphysema made the determination of the cardiothoracic ratio spurious. Nevertheless, in a large number of cases of this kind, even minor changes in the cardiac silhouette seen on fluoroscopic examination were of significance. Prominence of the area of the pulmonary artery or of the outflow portion of the right ventricle in the right anterior oblique position or displacement toward the apex of the point of opposite pulsation were the only changes indicative of enlargement of the right ventricle. Parkinson and Hoyle,[49] in a careful study of the pulmonary conus in emphysema, found evidence of dilatation on roentgenograms in 80 per cent of their cases. In none of our cases was enlargement of the left auricle, as evidenced by displacement of the barium-filled esophagus, noted.

Electrocardiographic tracings were available in 21 of the 60 cases in this series. In all of these, cardiac failure was present at the time the tracings were made. Voltage was low in 12 cases, moderately low in 4 and normal in 5. The most notable change was in the direction of electrical axis deviation. In 14 of the 21 cases definite deviation of electrical axis to the right was shown, while in 3 others there was revealed a tendency to deviation of the axis to the right, as evidenced by relatively deep S waves in lead I. In 3 cases there was no deviation of the axis, while in 1 case of paroxysmal ventricular tachycardia deviation of the axis to the left occurred just prior to the death of the patient.

DIAGNOSIS

It is significant that in not one case in this series was the diagnosis of cor pulmonale established or entertained prior to the onset of the symptoms and signs of cardiac failure. In all fairness, however, it should be stated that a great number of the patients did not seek medical attention until the distress of cardiac failure appeared.

It is obvious that from the point of view of treatment it is extremely important to detect the presence of cor pulmonale early, so that measures can be taken to ward off the development of cardiac failure. In this connection, it might be helpful to investigate routinely the cardiac status of all patients with chronic pulmonary disease and emphysema. Careful observations of physical signs indicative of increase in size of the right side of the heart, such as prominent impulse in the epigastrium and accentuation of the second pulmonic sound as well as careful ronetgenographic and fluoroscopic studies, are of great value. The presence of right axis deviation or the development of a deep

49. Parkinson, J., and Hoyle, C.: Heart in Emphysema, Quart. J. Med. **6**:59-86 (Jan.) 1937.

S wave in lead I, indicating a tendency toward right axis deviation, is of extreme value in establishing the diagnosis. In this connection the use of the special lead, as recommended by Goldberger,[50] for determining early changes in the right ventricle might be helpful.

Even after the development of cardiac failure, the diagnosis of cor pulmonale is too often missed. The suddenness of onset with severe dyspnea and precordial pain often leads to the erroneous diagnosis of coronary occlusion. In our series, this occurred 4 times. However, the evidences of purely right-sided failure, the "black cyanosis," the chemosis and edema of face and neck as well as the presence of emphysema or other extensive pulmonary disease, should suggest the diagnosis of cor pulmonale. Add to these the presence of polycythemia, deviation of the electrical axis to the right and absence of changes indicative of myocardial infarction on the cardiogram, and the diagnosis should be easily established.

Occasionally, in the presence of failure, murmurs appearing over the pulmonic area, both systolic and diastolic, have given rise to the erroneous diagnosis of rheumatic or congenital heart disease. In this series these diagnoses were made once each. In such cases the disappearance of the murmurs when compensation is restored and the absence of any cardiographic evidence of an enlarged left auricle should correct the error.

In this series the most common error in diagnosis was simply to denote them as cases of arteriosclerotic heart disease. This diagnosis was made in 26 cases. All too often this diagnosis is one of exclusion; that is, if congenital, rheumatic, hypertensive or thyrotoxic causes for heart disease are excluded, then arteriosclerosis remains. As all the patients in these cases were in the older age group, arteriosclerosis appeared to be a logical diagnosis. The occurrence of this error in almost 50 per cent of the cases serves only to emphasize the importance of considering chronic pulmonary disease as a significant etiologic factor in heart disease.

Of the 60 cases in this series, the correct diagnosis was made antemortem in 24 instances. It is interesting to note that the accuracy of diagnosis was greater in the more recent cases, indicating the increasing recognition of cor pulmonale in recent years.

CLINICAL COURSE, DURATION AND TYPE OF FAILURE

As mentioned previously, in none of the cases of cor pulmonale was the condition recognized prior to the onset of cardiac failure. Cardiac failure, predominantly of the right side, is the classic cardiac manifesta-

50. Goldberger, E.: The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy, Bull. New York Acad. Med. **20**:419-420 (July) 1944.

tion of the disease. The duration and number of episodes of cardiac failure were investigated. In 50 of the 60 cases the histories were adequate for study. Of the 50, it is significant that in 30 there was but one episode of cardiac failure, which terminated in death. It is difficult to describe each case in detail, but the composite picture is that of a person who has had chronic pulmonary disease for many years and in whom, over a period of but a few days to a week, an accentuation of cough rapidly developed. Many noted pain in the precordial or anterior area of the chest and a few noted pain in the upper part of the abdomen. Edema of the ankles, legs and thighs developed fairly rapidly soon after that. When brought to the hospital, these patients were acutely ill and in severe respiratory distress. Cyanosis was intense, and they fitted the descriptive term of "black cardiacs." Their faces were suffused; their eyes were injected and moist, and they were extremely restless and difficult to manage. In fact, some were definitely psychotic as a result of the cerebral anoxia. It is significant

TABLE 5.—*Incidence of Episodes of Failure*

Number of Patients	Episodes of Failure
30	1
11	2
1	3
2	4
4	0 (Died of encephalitis, meningitis and pneumonia)
10	? (Undetermined number, language difficulty, coma, etc.)

that there seemed to be more than a coincidental relation between the administration of a sedative and the occurrence of death in a few cases.

In 7 of these cases, death occurred within a period of one to three days from the onset of failure, while in the remainder the duration of life varied from three weeks to six months. The mode of death for most of the patients was gradual, although a large number died relatively suddenly. It was commonly observed that while clinically the patients appeared to be comfortable, or even at times improving, they died suddenly, for no apparent reason. This observation was also made by Scott and Garvin [14] and by Brill.[46]

Eleven patients had two episodes of failure prior to death, while 1 had three and 2 four such episodes. In some of these cases there were intervals of as long as two years between episodes of failure, while in 1 case a period of five years elapsed before death occurred. These cases indicate the importance of the interrelation between pulmonary insufficiency and cardiac failure, for the cardiac insufficiency was probably secondary to the anoxia produced by an intercurrent

pulmonary pathologic process, such as bronchopneumonia. When this subsides, cardiac compensation can often be restored and maintained as long as pulmonary ventilation and respiratory exchange is adequate.

The type of failure in all the cases was predominantly right-sided failure, with the exception of 3 cases in which paroxysmal nocturnal dyspnea was present. This evidence of additional left-sided failure may be attributed to unrecognized sclerosis of the smaller coronary vessels, to the possibility of an unrecognized preexistent hypertension or else to the fact that in cor pulmonale the patient often suffers from a severe degree of chronic anoxia, which reflects itself in an insufficient oxygenation of the blood that, in turn, results in anoxemia of both ventricles.

TREATMENT

The management of cor pulmonale resolves itself basically into the prevention and treatment of anoxemia. It is apparent, therefore, that all efforts should be made to promote the efficiency of the respiratory mechanism and to minimize so far as is possible the damage already present in the lungs.

It is beyond the scope of this paper to discuss the treatment of the various types of pulmonary lesions which may play a part in the causation of cor pulmonale. Nevertheless, it is important that all patients with bronchial asthma, chronic bronchitis, bronchiectasis and suppurative pulmonary infection be treated vigorously early in the course of the disease in order to prevent the development of hypertrophy of the right ventricle. The management of these conditions has been ably described by other authors dealing with these subjects.

When pulmonary emphysema and pulmonary fibrosis have been established, efforts should be directed toward the improvement of respiratory exchange and the prevention of bronchial and pulmonary infections. In this regard, it is important that these patients be impressed with the fact that all of the infections of the respiratory tract, no matter how mild they may appear to be, should not be treated lightly. These patients should be cautioned against undue exposure to inclement weather and to crowds during epidemic times. As most of our patients seem to have done better during the summer months, it would appear wise whenever possible to send them to less rigorous climates during the winter months. For some, a permanent relocation in a milder climate may do more to lengthen their lives than any other procedure.

For obese patients with considerable dyspnea and emphysema, the use of an abdominal belt may add considerably to their comfort.

As was pointed out elsewhere in this paper, it is often difficult to determine clinically in cases of cor pulmonale the onset of cardiac failure. Consequently, in recent years we have been digitalizing our patients before the signs of right-sided failure become manifest. In this way,

we feel that we may be delaying somewhat the onset of cardiac insufficiency. When the signs of right-sided failure appear, the patient is immediately placed on a regimen of a salt-free diet and restricted fluids, and diuretics are administered when necessary.

Cardiac failure in cor pulmonale is often acute, and death may occur within a few days. These cases should be treated as emergencies, and all measures aimed at combating anoxemia and cardiac failure should be taken without delay. Oxygen is vitally important and, in our experience, is best administered under positive pressure in high concentration by means of a special mask. Digitalization should be immediate and complete. Diuretic measures should be administered vigorously. Mercurial diuretics can be used freely and administered once daily if necessary. When polycythemia is evident, withdrawal by phlebotomy of 500 to 1,000 cc. of blood may be a life-saving procedure.

As indicated elsewhere in this paper, these patients are usually extremely restless and often disoriented. Sedation must be used with extreme caution. Morphine and codeine are to be avoided assiduously. Many patients may appear more comfortable after their administration, but few recover afterward. By suppressing the cough reflex, the purulent bronchial secretions are permitted to puddle in the pulmonary tree, further increasing anoxemia. Paraldehyde is not recommended, because it is largely excreted by and is irritating to the lungs. Chloral hydrate and barbiturates may be used with caution if it is remembered that in older patients the sedatives of the latter group may be exciting. In the final analysis, the cerebral manifestations result from cerebral anoxemia, which will be relieved only after measures aimed at combating the pulmonary infection and cardiac failure take effect.

COR PULMONALE AND OTHER CARDIAC DISEASE

This paper has dealt with cases of cor pulmonale unassociated with other cardiac disease. In the past ten years, we have become more and more impressed with the prevalence of this condition both clinically and in the autopsy room. Only too often the attention of the clinician and pathologist is diverted by the presence of hypertension or coronary arteriosclerosis as the primary factor in a given case, so that the cor pulmonale which may also be present is minimized or completely overlooked. In many of these cases, a review of the clinical history will often reveal that the cor pulmonale, with its associated pulmonary lesion, played a relatively larger part in the symptoms and disability than the coincidental hypertension or arteriosclerosis. It is evident from the statistics presented in this paper that the greater number of cases of cor pulmonale occur in the same age group that is subject to both hypertension and arteriosclerosis.

SUMMARY

Sixty consecutive cases of cor pulmonale unassociated with other forms of heart disease were studied at necropsy.

The underlying etiologic factors may originate primarily in the bony thorax, in the pulmonary vascular tree or in the pulmonary parenchyma.

Diffuse obstructive emphysema, either primary or secondary to such diseases as pulmonary tuberculosis or silicosis, was considered to be the significant underlying pulmonary factor in the vast majority of the cases.

Diffuse obstructive emphysema was thought to produce a changed pressure relation within the alveoli and in this manner result in an increased resistance to the flow of blood to the lungs. This change was considered to be a primary mechanism in the development of cor pulmonale, while such associated factors as anatomic obliteration of the pulmonary vascular bed, fibrosis of the lung, compensatory polycythemia and overfilling of the heart were considered to be secondary aggravating factors of varying significance.

The clinical course in these 60 cases was studied, and the difficulty and importance of diagnosis in the prefailure stage was emphasized.

Treatment of cor pulmonale was considered in general terms.

ABNORMALITIES IN THE ELECTROCARDIOGRAM FOLLOWING HEMOLYTIC STREPTOCOCCUS SORE THROAT

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AN extensive study has been made recently of acute hemolytic streptococcic disease of the respiratory tract among military personnel. A summary of the clinical and bacteriologic observations, so far as they contribute to the understanding of the etiology and pathogenesis of rheumatic fever, has been published.[1] The data indicated (1) that rheumatic fever was invariably preceded by infection by group A hemolytic streptococci; (2) that a nonarthritic nonsuppurative continuing disease also frequently followed infection by these organisms, and (3) that electrocardiographic abnormalities, indicating the presence of carditis, were often present during the course of arthritic and nonarthritic illness.

It is the purpose of this paper to illustrate and describe the electrocardiographic abnormalities that were discovered and to compare them with those previously observed during the course of streptococcic and other types of infectious disease.

MATERIAL AND METHODS

All patients suffering from disease of the respiratory tract were seen by one of us; a history was obtained, a physical examination performed and culture materials taken from the throat.[1a] Patients discovered on clinical and bacteriologic grounds

The facilities of the Department of Medicine, Stanford University School of Medicine, San Francisco, were made available to the commission for certain purposes.

These studies were made during a field study by the Commission on Hemolytic Streptococcal Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

1. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: The Etiology and Pathogenesis of Rheumatic Fever, Arch. Int. Med. **76**:131 (Sept.) 1945.

1a. Serial antibody determinations were made in nearly all these cases. A significant antistreptolysin and/or antifibrinolysin response occurred in approximately 87 per cent.

to be infected by group A hemolytic streptococci were studied by a variety of laboratory procedures. Most important, from the standpoint of this report, were serial determinations of the erythrocyte sedimentation rate (Westergren) and electrocardiograms, each of which was obtained on approximately the ninth and twenty-first days of the illness and more frequently and for a longer period in many instances. Certain patients have been included for whom this program was not followed precisely. No patient received digitalis.

RESULTS

Detailed serial observations were available on 185 patients with acute hemolytic streptococcic disease of the respiratory tract, approxi-

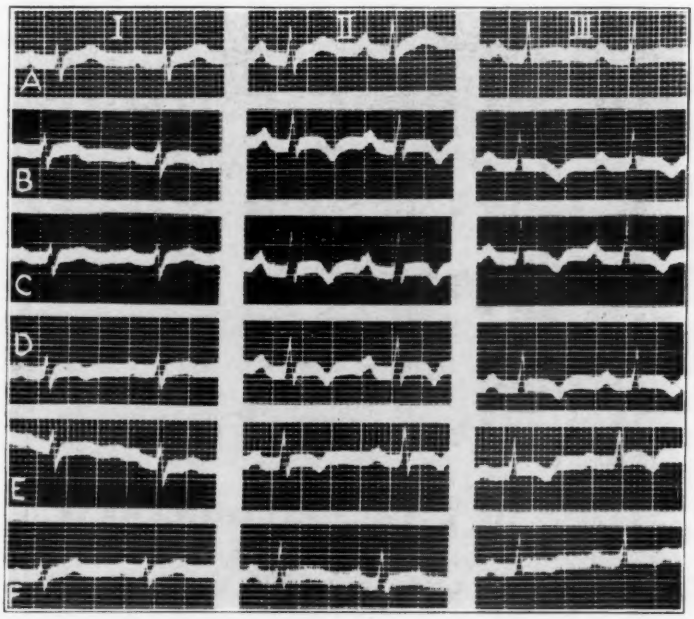

Fig. 1 (case 1).—Nonarthritic continuing disease. There was prolongation of the PR interval on the ninth day and later. There were progressive changes in the T waves, with flattening in lead I and inversion in leads II and III followed by a return toward normal. *A*, the ninth day, with the erythrocyte sedimentation rate 86 mm. per hour. *B*, the fifteenth day, with the erythrocyte sedimentation rate 90 mm. per hour. *C*, the twentieth day, with the erythrocyte sedimentation rate 84 mm. per hour. *D*, the twenty-fourth day, with the erythrocyte sedimentation rate 42 mm. per hour. *E*, the thirty-third day, with the erythrocyte sedimentation rate 24 mm. per hour. *F*, the forty-first day, with the erythrocyte sedimentation rate 23 mm. per hour.

mately 50 of whom exhibited signs of an arthritic or nonarthritic continuing disease. Definite electrocardiographic abnormalities were discovered in 31, and these patients are the subjects of this report.

Pertinent Data in Thirty-One Cases of Hemolytic Streptococcus Disease of the Respiratory Tract in which Abnormalities of the Electrocardiogram Were Demonstrated

	Acute Sore Throat					Arthritis		PR Interval			
Case Number	Day First ECG	Days Afebrile First ECG	Day First Abnormal ECG	Duration of ECG Abnormality in Days	ESR Abnormal in Days	Present	Days ECG Abnormal Before Appearance	Maximum Duration Observed in Seconds	Minimum Duration Observed in Seconds	T Wave	Comment
1	9	4	9	28	>41	No	—	0.24	0.18	Inverted in leads I, II, III	Illustrated
2	12	3	12	>20	>20	No	—	0.24	0.21	Normal	
3	10	4	10	> 7 <25	<15	No	—	0.18	0.18	Inverted in leads I, II, III	Illustrated
4	28	20	28	<14	45	No	—	0.24	0.16	Normal	
5	9	6	9	<18	<21	No	—	0.14	0.14	Flat, lead II; inverted, lead III	T waves became upright in leads II and III during convalescence
6	13	4	32	>12	>45	No	—	0.21	0.16	Normal	
7	9	3	9	10	20	No	—	0.16	0.16	Flat. lead I; inverted, II and III	Illustrated
8	7	4	7	>21	>28	No	—	0.24	0.21	Normal	
9	24	F	24	>19	43	No	—	0.36	0.24	Normal	Illustrated
10	13	10	13	>20	>33	No	—	0.26	0.22	Normal	
11	14	2	14	> 8	<21	No	—	0.24	0.24	Normal	
12	8	6	8	>14	15	No	—	0.16	0.16	Inverted in leads II and III	T waves became upright in leads II and III during convalescence
13	9	F	9	>24	>28	No	—	0.24	0.19	Inverted in leads II and III	Illustrated

14	11	8	17	<13	>30	No	—	0.21	0.16	Normal	
15	11	22	29	< 7	>45	No	..	0.22	0.16	Normal	
16	8	5	8	>36	>36	No	—	0.16	0.16	Inverted in leads I, II, III	ECG remained abnormal through 36th day
17	9	F	25	<19	>44	No	—	0.22	0.16	Normal	Continuing illness with fever
18	9	36	40	?	>40	No	—	0.24	0.16	Normal	No ECG obtained between 9th and 40th days
19	13	9	13	>38	>50	No	—	0.24	0.24	Normal	
20	13	9	13	<11	<10	No	—	0.18	0.18	Flat in lead II; inverted lead III	T waves, leads II and III, upright on 25th day
21	38	34	38	7	>39	No	—	0.21	0.16	Normal	
22	8	5	8	3	<12	No	—	0.16	0.16	Flat in leads I, II and III	T waves of high voltage by 12th day
23	8	F	14	>10	50	Yes	N.D.	0.36	0.16	Normal	Moderately severe rheumatic fever
24	10	F	23	70	90	Yes	60	0.28	0.16	Inverted in leads I, II and III	Illustrated
25	19	F	19	> 7	45	Yes	N.D.	0.24	0.16	Normal	Severe rheumatic fever
26	36	16	36	50	85	Yes	27	0.16	0.16	Flat, lead I; inverted II and III	Illustrated
27	10	4	10	10	70	Yes	0	0.24	0.16	Normal	Mild rheumatic fever
28	7	5	7	35	40	Yes	5	C.B.	0.16	Flat, leads I and II; inverted, lead III	Illustrated
29	—	—	—	8	—	Yes	N.D.	0.24	0.16	Normal	Repeated sore throats before onset of rheumatic fever; several relapses
30	9	6	9	>150	70	Yes	6	0.16	0.16	Inverted, leads I, II and III	Severe rheumatic fever with pericarditis
31	36	F	36	35	45	Yes	N.D.	0.36	0.16	Normal	Mild rheumatic fever

Explanation of abbreviations: N.D., not done; F, fever; C.B., complete block.

The essential data are presented in the table. Only a prolongation of the PR interval to more than 0.2 second was regarded as significant under any circumstances. Unless the conduction time was demonstrated on either previous or subsequent occasions to be at least 0.05 second less, a PR interval of 0.24 second was required as an index of abnormality. Changes in the elevation of the RS-T segment were ignored. The T waves were regarded as normal unless they were completely flat or inverted in leads I or II. Variations in the form of the T wave in lead III were not considered unless one or both of the other leads exhibited abnormalities. Precordial leads were not utilized.

The application of these relatively rigorous criteria has eliminated certain cases in which the electrocardiogram would usually be regarded

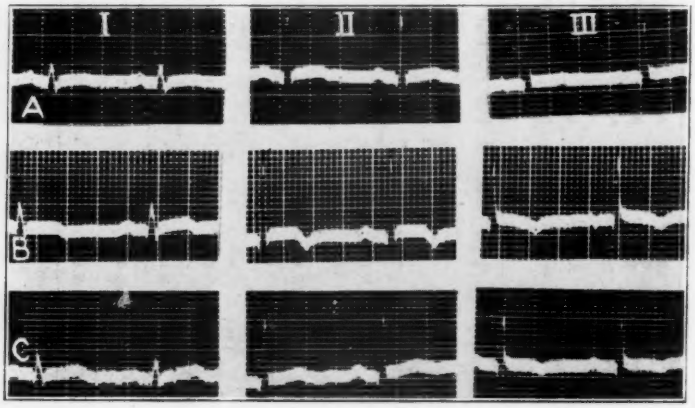

Fig. 2 (case 3).—Nonarthritic continuing disease. *A*, the tenth day, with the erythrocyte sedimentation rate 84 mm. per hour. The T waves were flattened in all leads. *B*, the sixteenth day, with the erythrocyte sedimentation rate 11 mm. per hour. The T waves were inverted in all leads. *C*, the thirty-fifth day, with the erythrocyte sedimentation rate 10 mm. per hour. The T waves were of low voltage but were upright in leads I and II and inverted in lead III.

as abnormal. It was believed that the technic of interpretation described here would be more clearcut and less controversial.

Nonarthritic Continuing Disease. — Abnormal electrocardiograms were obtained for 22 patients with nonarthritic, poststreptococcic continuing disease. In 15, there was a significant prolongation of the PR interval. The T wave was inverted in leads I, II and III in 3, inverted in leads II and III in 2, flat in all three leads in 1, flat in lead I and inverted in leads II and III in 1 and flat in lead II and inverted in lead III in 2. The PR interval was prolonged in 2 patients whose T waves were abnormal.

The electrocardiograms obtained in cases 1, 3, 7, 9 and 13, accompanied with a brief clinical description, are illustrated (figs. 1, 2, 3, 4 and 5).

Electrocardiograms were obtained as early as nine days after the onset of the acute streptococcic illness of the respiratory tract for 10 of the patients. Abnormalities that persisted for three to more than twenty-eight days were discovered in 8 on the first examination. All but 1 of these patients had been afebrile for three to six days at this time.

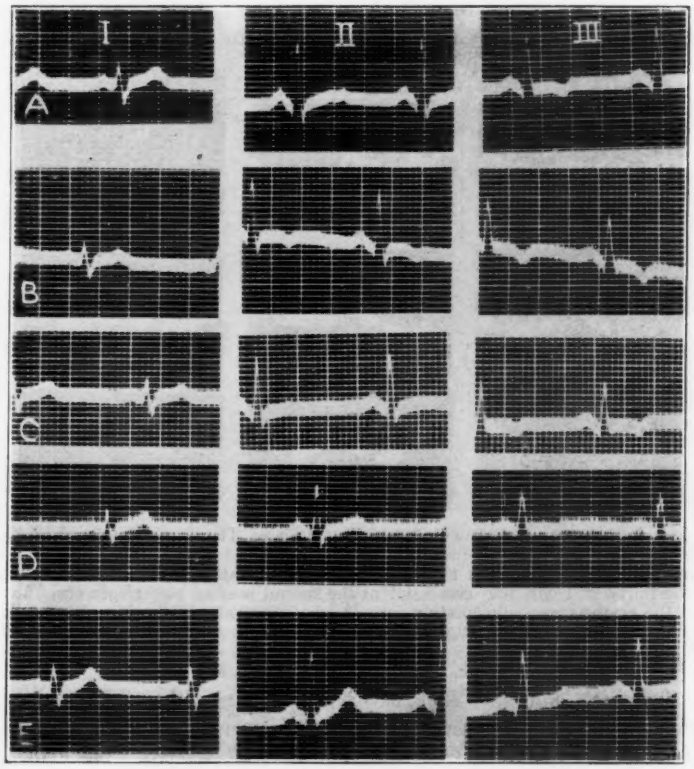

Fig. 3 (case 7).—Nonarthritic continuing disease. There were progressive changes in the T waves from the ninth day, with a return to normal. There was partial flattening in lead I and inversion in leads II and III. *A*, the ninth day, with the erythrocyte sedimentation rate 68 mm. per hour. *B*, the fourteenth day, with the erythrocyte sedimentation rate 48 mm. per hour. *C*, the eighteenth day, with the erythrocyte sedimentation rate 20 mm. per hour. *D*, the twenty-third day, with the erythrocyte sedimentation rate 15 mm. per hour. E, the thirty-fourth day, with the erythrocyte sedimentation rate 25 mm. per hour.

Nine additional patients were studied for the first time on the tenth to fourteenth days, and the initial electrocardiograms were abnormal for 6.

Insufficient serial examinations were performed to determine the precise duration of the electrocardiographic abnormalities. They were observed to persist for seven or more days in 15 patients, for fourteen or more days in 9, for twenty or more days in 7 and for twenty-eight or more days in 3.

That a continuing tissue reaction was established in these patients is further emphasized by the duration of abnormal erythrocyte sedimentation rates (more than 20 mm. per hour) that were present for fourteen days in 21, for twenty days in 16, for thirty days in 13, for 40 days in 8 and for fifty or more days in 1.

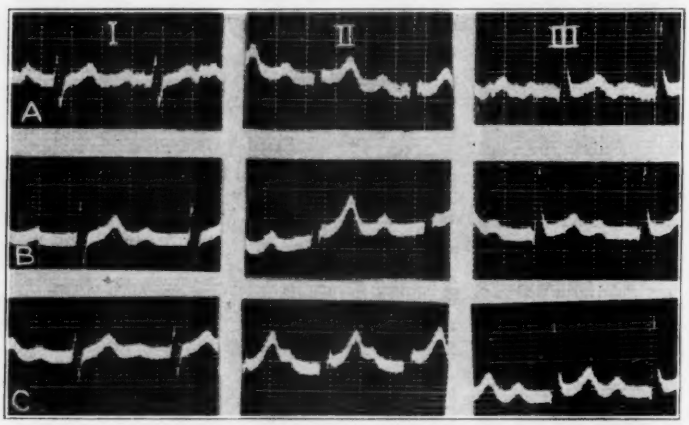

Fig. 4 (case 9).—Nonarthritic continuing disease. There was definite prolongation of the PR interval. *A*, the twenty-fourth day, the fifth day of the first bout of poststreptococcic fever, with the erythrocyte sedimentation rate 50 mm. per hour. *B*, the thirty-first day, the second day of the second bout of poststreptococcic fever, with the erythrocyte sedimentation rate 22 mm. per hour. *C*, the forty-second day, with the erythrocyte sedimentation rate 20 mm. per hour; the patient was afrebile and working.

Arthritic Continuing Disease.—Nine patients with poststreptococcic arthritic continuing disease (rheumatic fever) were observed for whom abnormalities in the electrocardiogram were discovered. No evidence of carditis was present in 7 similar patients.

The abnormalities were similar to those just described. The T waves were flat or inverted in 4, in 2 of which there was also exhibited prolongation of the PR interval. A conduction defect was demonstrated in the other 5 patients which was somewhat more marked than that usually present in the nonarthritic disease. Complete heart block occurred once.

Arthritic poststreptococcic disease was more severe than the nonarthritic type, as indicated by the more prolonged duration of abnormalities in the electrocardiogram and in the erythrocyte sedimentation rate, but it must be emphasized that there was overlapping between the two groups in this respect.

Electrocardiograms were obtained in 4 cases five, six, twenty-seven and sixty days before the onset of arthritis, and abnormalities were discovered in each on the first examination.

Cases 24, 26 and 28 are illustrated and described (figs. 6, 7 and 8).

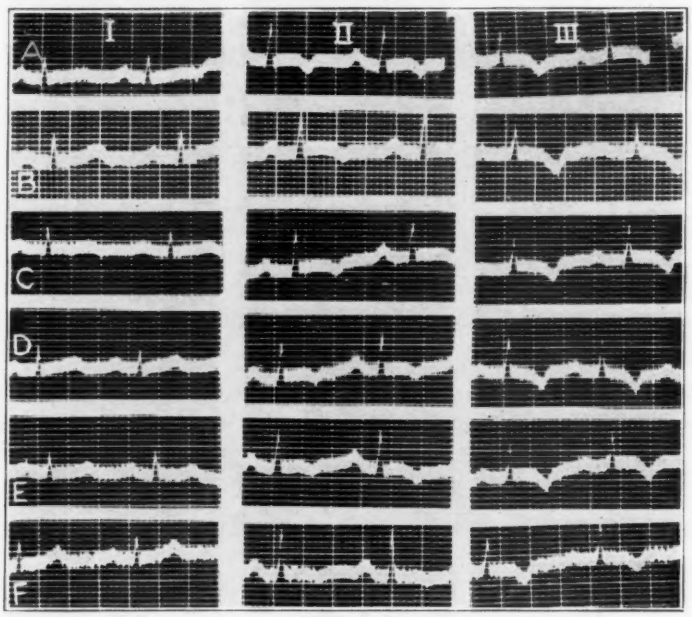

Fig. 5 (case 13).—Nonarthritic continuing disease. There was prolongation of the PR interval and progressive changes in the T waves. There was flattening in lead I and inversion in leads II and III. The conduction time returned to normal, but the T waves did not. *A*, the ninth day, with the erythrocyte sedimentation rate 50 mm. per hour; the patient was febrile. *B*, the fourteenth day, with the erythrocyte sedimentation rate 30 mm. per hour; the patient had been afrebile for twenty-four hours. *C*, the nineteenth day, with the erythrocyte sedimentation rate 44 mm. per hour. *D*, the twenty-fourth day, with the erythrocyte sedimentation rate 35 mm. per hour. *E*, the twenty-eighth day, with the erythrocyte sedimentation rate 28 mm. per hour. *F*, the thirty-third day, with the erythrocyte sedimentation rate 6 mm. per hour.

COMMENT

This study has revealed that definite electrocardiographic evidence of carditis may be demonstrated in many persons who have undergone an acute group A hemolytic streptococcic infection of the respiratory

tract. Prolongation of the PR interval or abnormalities in the T waves or both were discovered.

The presence of carditis was invariably associated with other evidence of a continuing abnormal tissue reaction. In some cases an elevated erythrocyte sedimentation rate was the only sign of an active process; in others, fever and malaise were present, and

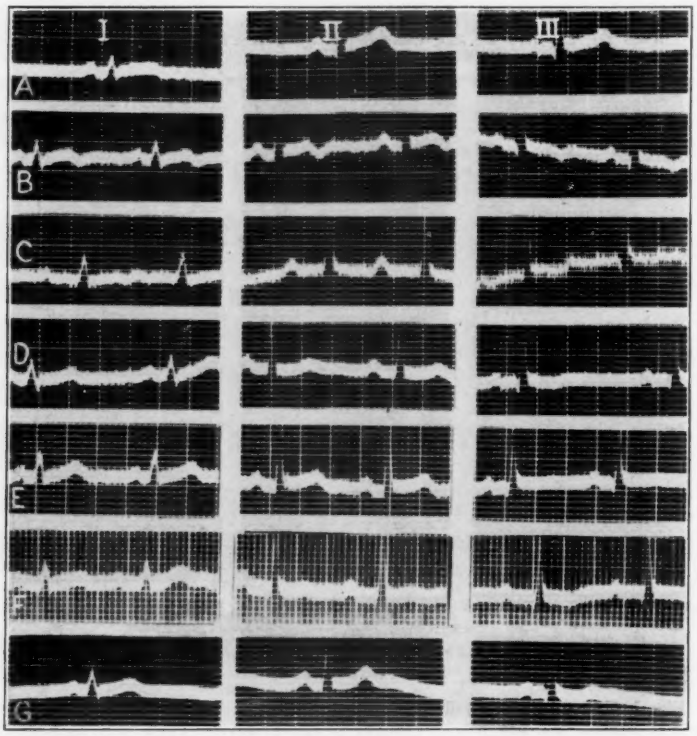

Fig. 6 (case 24).—Nonarthritic continuing disease followed by development of arthritis. *A*, the tenth day, with the erythrocyte sedimentation rate 50 mm. per hour and the electrocardiogram normal. *B*, the twenty-third day, with the erythrocyte sedimentation rate 89 mm. per hour, marking the onset of nonarthritic poststreptococcic fever. The T waves were inverted in all leads. *C*, the twenty-eighth day, with the erythrocyte sedimentation rate 107 mm. per hour, the sixth day of the poststreptococcic fever. The PR interval was 0.32 seconds. *D*, the thirty-fourth day, with the erythrocyte sedimentation rate 85 mm. per hour. The patient had been afrebile for four days. There was a slight flattening of the T waves in all leads. *E*, the forty-seventh day, with the erythrocyte sedimentation rate 65 mm. per hour. The electrocardiogram was approximately normal. *F*, the ninetieth day, with the erythrocyte sedimentation rate 35 mm. per hour, eight days after the onset of arthritis. The PR interval was 0.22 seconds. *G*, the one hundred and eighteenth day, with the erythrocyte sedimentation rate 15 mm. per hour and the electrocardiogram normal.

in a few arthritis also appeared. When arthritis was present, the clinical syndrome was similar in every respect to that associated with typical rheumatic fever. The illness was frequently prolonged, and this was more often the case if the joints were involved. There was, however, much overlapping, both in severity and duration, and it seems quite impossible to establish adequate criteria for the sharp differentiation between arthritic and nonarthritic nonsuppurative poststreptococcic continuing disease. The fact that carditis was present soon after the acute illness of the respiratory tract had subsided and days to weeks

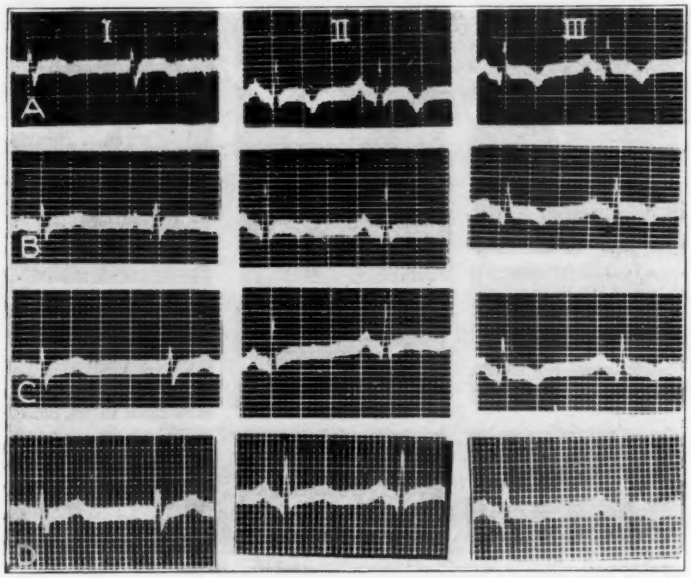

Fig. 7 (case 26).—Nonarthritic continuing disease followed by the development of arthritis. *A*, the thirty-sixth day, with the erythrocyte sedimentation rate 38 mm. per hour, twenty-seven days before the onset of arthritis. The T waves were inverted in leads I, II and III. *B*, the seventy-third day, with the erythrocyte sedimentation rate 80 mm. per hour, ten days after the onset of arthritis. The T waves were returning to normal. *C*, the eightieth day, with the erythrocyte sedimentation rate 50 mm. per hour. The T waves were more nearly normal. *D*, the one hundred and eighth day, with the erythrocyte sedimentation rate 15 mm. per hour. The T waves were approximately normal.

before articular involvement was manifest is of importance. Various aspects of this subject have been discussed in detail elsewhere.[1]

It is necessary for the purpose of this report only to determine whether the described electrocardiographic abnormalities are unique to the poststreptococcic state and if they are similar to those previously observed in rheumatic fever. Several reports are available that

describe the relatively frequent occurrence of electrocardiographic abnormalities following a hemolytic streptococcus disease of the respiratory tract, usually scarlet fever. Roelsen,[2] in an extensive survey, discovered both changes in the T wave, which were more likely to occur early, and prolongation of the PR interval. The latter abnor-

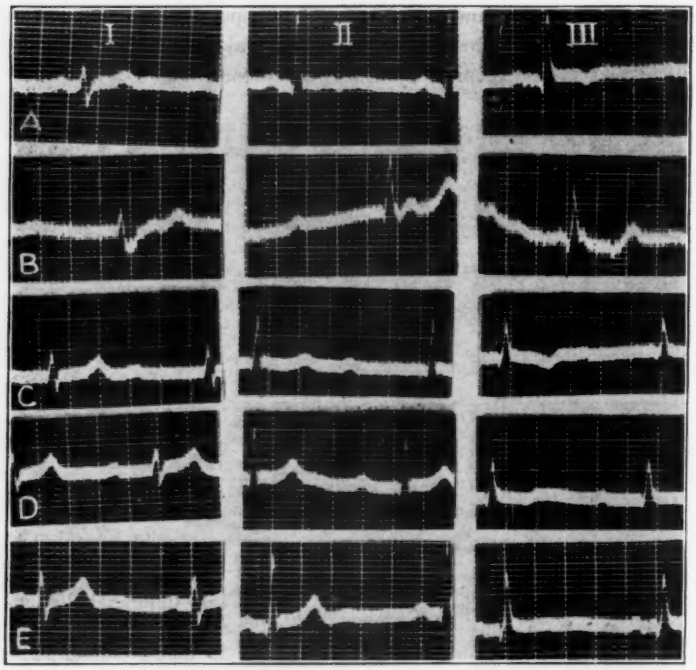

Fig. 8 (case 28).—Arthritic continuing disease. *A*, the seventh day, with the erythrocyte sedimentation rate 30 mm. per hour, five days before the onset of poststreptococcic fever. The T waves were flat or inverted in all leads. *B*, the nineteenth day, with the erythrocyte sedimentation rate 90 mm. per hour, seven days after the onset of poststreptococcic fever and the first day of arthritis, which was minimal. Complete heart block was present. *C*, the twenty-seventh day, with the erythrocyte sedimentation rate 50 mm. per hour, the PR interval greatly prolonged and the T waves returning to normal. *D*, the twenty-ninth day, with the erythrocyte sedimentation rate 50 mm. per hour, the PR interval shortening and the T waves about normal. *E*, the ninetieth day, with the erythrocyte sedimentation rate 10 mm. per hour and the electrocardiogram normal.

mality was more frequently observed and was more pronounced in arthritic patients. The observations of Faulkner, Place and Ohler[3]

2. Roelsen, E.: Electrocardiographic Studies in Scarlet Fever, Acta med. Scandinav. **106**:26, 1941.

3. Faulkner, J. M.; Place, E. H., and Ohler, W. R.: The Effect of Scarlet Fever on the Heart, Am. J. M. Sc. **189**:352, 1935.

were similar, except that all the electrocardiograms obtained before the thirteenth day of the acute disease of the respiratory tract were normal. This result was in striking contrast with the results of this study.

Descriptions of electrocardiograms obtained during and after the course of other acute infectious diseases are few and incomplete, Master, Romanoff and Jaffe [4] described conduction defects and changes in the T wave in a significant percentage of all cases of typhoid, typhus, gonococcic arthritis, pulmonary tuberculosis, malaria, rheumatoid arthritis and lobar pneumonia. Only in connection with the last disease was the natural history of the electrocardiographic abnormalities described in detail. Definite changes in the T wave were present only during the acute febrile phase of the illness. The PR interval was greater than 0.20 second in 11 per cent of all cases. In this small group the abnormality appeared late in the course of the disease and persisted throughout convalescence.

A few other papers [5] described abnormal electrocardiograms following "influenza." In the absence of more definite information, it is possible that this disease was actually hemolytic streptococcus infection of the respiratory tract. Bang [6] has stated that conduction defects may occur in association with gonorrheal arthritis.

Electrocardiographic abnormalities essentially similar to those described in this paper have been observed recently following epidemic parotitis (mumps).[7] The changes were present early in the illness and were transitory, persisting for only four to eight days in most instances.

The available information indicates that abnormalities of the electrocardiogram of the type that were discovered during the poststreptococcic state may also be observed during and after attacks of other infectious diseases. Definite statements are not available which permit an evaluation of the circumstances under which they may occur in relation to nonstreptococcic infections. It seems probable that the frequency, duration and magnitude of the abnormalities will be greater after an infection by hemolytic streptococci, but true specificity of the observed changes cannot be established.

4. Master, A. M., and Jaffe, H.: Electrocardiographic Evidence of Cardiac Involvement in Acute Disease, Proc. Soc. Exper. Biol. & Med. **31**:931, 1934. Master, A. M.; Romanoff, A., and Jaffe, H.: Electrocardiographic Changes in Pneumonia, Am. Heart J. **6**:696, 1931.

5. Burnett, C. T., and Piltz, G. F.: The Electrocardiogram in the Acute Infections, J. A. M. A. **93**:1120 (Oct. 12) 1929. Hyman, A. S.: Post-Influenzal Heart Block, M. J. & Rec. **124**:698, 1926.

6. Bang, O.: Gonorrheal Myocarditis, Brit. M. J. **1**:117, 1940.

7. Rosenberg, D. H.: Electrocardiographic Changes in Epidemic Parotitis (Mumps), Proc. Soc. Exper. Biol. & Med. **58**:9, 1945.

Few comprehensive studies of the electrocardiogram in connection with acute rheumatic fever have been published. Prolongation of the PR interval,[8] heart block,[9] "coronary type" T waves[10] and variations in the QRST segment with pericarditis[11] have been described. It is common knowledge that all these variations from the normal may occur, but precisely how frequently, to what degree and in what combination could not be ascertained.

In Wilson's group of 54 cases,[12] prolongation of the PR interval was most commonly observed, but changes in the T wave also occurred. Pardee[13] stated: "If frequent records are taken during the acute stage of this disease (rheumatic fever) more than 60 per cent of cases will be found to show inversion or other abnormalities of the T wave such as have been described as resulting from myocardial disease. A large number will show variations in the duration of the auriculoventricular conduction time . . . Many will show both of these types of electrocardiographic change."

It is proper to conclude that the abnormalities of the electrocardiogram observed during this study of the nonsuppurative complications of acute hemolytic streptococcus infection of the respiratory tract were similar to those usually associated with rheumatic fever. This evidence adds weight to the conclusion that poststreptococcic continuing disease with arthritis was a tissue reaction identical with that ordinarily described as rheumatic fever and that the nonarthritic illness was a closely related process.

SUMMARY

A nonsuppurative continuing disease, often associated with abnormalities of the electrocardiogram, commonly follows acute group A hemolytic streptococcus disease of the respiratory tract. Arthritis may or may not accompany this process.

Prolongation of the PR interval and flattening and inversion of the T waves were observed.

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8. Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, J. Exper. Med. **39**:1, 1924.

9. Wedd, A. M.: Complete Heart Block in Rheumatic Fever, Am. Heart J. **14**:759, 1937.

10. Porte, D., and Pardee, H. E. B.: The Occurrence of the Coronary T Wave in Rheumatic Pericarditis, Am. Heart J. **4**:584, 1929.

11. Bellet, S., and McMillan, T. M.: Electrocardiographic Patterns in Acute Pericarditis, Arch. Int. Med. **61**:381 (March) 1938.

12. Wilson, M. G.: Rheumatic Fever, New York, Commonwealth Fund, 1940.

13. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, New York, Paul B. Hoeber, Inc., 1941.

The changes in the electrocardiogram were similar in nonarthritic and in arthritic cases, but they were more definite and persisted for longer periods if the joints were involved.

The observed electrocardiographic abnormalities are not unique to the poststreptococcic state but are identical with those previously discovered during the course of acute rheumatic fever.

Progress in Internal Medicine

BLOOD

A Review of the Recent Literature

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INFECTIOUS MONONUCLEOSIS

An increasing number of papers are appearing in the literature dealing with infectious mononucleosis, which is a malady of unusual interest chiefly because of its tendency to simulate so many other disease syndromes with its diverse symptoms, because there is still considerable doubt concerning its causation and its pathologic changes and because of the unique presence of sheep cell agglutinins in the blood of patients with this disease.

Attempts have been made by Julianelle, Bierbaum and Moore [215] to transmit infectious mononucleosis to rabbits and monkeys and, to a lesser extent, to white mice, guinea pigs and human beings. Specimens of blood were withdrawn from 15 patients during the febrile stage, on the second to the seventh day after the onset, except in 1 instance in which the collection was made on the tenth day of illness, after two days of normal temperature. Experiments were controlled with blood from 3 patients with streptococcic septicemia and pneumonitis of unknown cause and Rocky Mountain spotted fever. An effort was also made to transmit the disease with washings obtained by gargling with 25 to 50 cc. of isotonic solution of sodium chloride before breakfast. Four of these experiments were carried out, in which 16 rabbits and 4 monkeys were employed. Three experiments were done with excised tissue from the lymph nodes in an attempt to transmit the disease to monkeys and rabbits. In addition, the material from 2 other lymph nodes prepared in a similar manner was given to 2 healthy human

215. Julianelle, L. A.; Bierbaum, O. S., and Moore, C. V.: Studies on Infectious Mononucleosis, Ann. Int. Med. **20**:281, 1944.

volunteers, neither of whom had any knowledge of having previously had infectious mononucleosis. In brief, it was found that a distinct tendency toward leukocytosis, with increases in both lymphocytes and monocytes, occurred in the animals but that in no case did the leukocytes present the characteristics of those seen in patients with infectious mononucleosis. Furthermore, the controlled observations indicated strongly that the changes in the blood were a nonspecific response possibly to foreign proteins. There were no cytologic changes observed in any of the 4 human volunteers who served as subjects for experiments. Furthermore, there was no evidence to indicate the development of heterophile antibodies in any of the animals, as only a relatively small proportion showed a low and transitory increase in titer. Attempts to demonstrate the virus by propagation in eggs led to the conclusion that either it was not present in the material employed or this medium does not support its growth. Attempts to transmit the disease to human beings were unsuccessful. Two subjects gargled with throat washings from 1 patient, and 2 others permitted the intramuscular injection of a saline extract from cervical lymph nodes removed from patients during the febrile period of the disease. Also, 1 of these 2 subjects sprayed the nasopharynx with a portion of the saline extract. In no instance did hematologic changes result which indicated that transmission had occurred. Although previous reports indicate that infectious mononucleosis may be due to a filterable virus, there is nothing in these experiments, which seem to have been carried out rather carefully, to substantiate this theory. There is apparently, therefore, an inconsistency between the results reported in the literature and of these experiments which further investigation alone can resolve.

One of the few fatal cases of infectious mononucleosis in which there has been a careful pathologic examination of the tissues is reported by Ziegler.[216] The patient was a 22 year old white woman who suddenly died, after an illness of between three and four weeks, in a state of severe shock as the result of spontaneous rupture of the spleen. There are now on record 3 cases of ruptured spleen resulting from this disease, and of the 3 patients 1 died and the other 2 were saved by surgical intervention. The pathologic study indicates that infectious mononucleosis is an acute or subacute infectious disease of unknown cause, having many diverse clinical and pathologic manifestations. The essential pathologic lesions of infectious mononucleosis are focal lesions in the various organs of the body, especially the liver, kidneys, lymph nodes and spleen. Ziegler regards it as a generalized infection with specific localization in one or more of the tissues or

216. Ziegler, E. E.: Infectious Mononucleosis: Report of Fatal Case with Autopsy, Arch. Path. **37**:196 (March) 1944.

organs of the body. Various lesions have formerly been described in the lymph nodes, the spleen, the tonsils and the marrow. To these have been added the changes in the liver, the kidneys, the spleen and the lungs of the patient reported by Ziegler. According to this observer, the monocytes cannot be distinguished in tissue sections from the peculiar large lymphocytes as readily as in stained blood smears. In addition, the lesions, especially those in the spleen, contain large cells which one might classify as lymphoblasts, clasmatocytes or stem cells. The edema, the cloudy swelling and the infiltrative changes found in the liver and the spleen explain the enlargement of these organs. The jaundice, which occurs not uncommonly, may be explained on the basis of profuse focal hepatitis, which is a somewhat better hypothesis than that of swelling of the lymph nodes in the region of the bile duct, at least in those cases in which the enlarged liver is present. Although Ziegler did not obtain nerve tissue for study, he states that one could readily imagine full-sized mononuclear infiltration in the central nervous system or perhaps merely edema and obstruction of capillaries, such as he demonstrated in the lung, as the basis for neurologic manifestations.

A 33 year old man with infectious mononucleosis whose spleen spontaneously ruptured is reported on by Darley, Black, Smith and Good.[217] It is of special interest that pathologic studies of the spleen were made and reported. This patient had the characteristic clinical signs of infectious mononucleosis with two interesting features—he was jaundiced and had severe abdominal pain requiring morphine for relief. On the sixteenth day of the illness the patient was awakened from sleep suddenly by a stabbing agonizing pain in the midepigastrium and back. He went into a state of shock almost immediately. Laparotomy revealed a large tear near the hilus of the spleen which necessitated splenectomy. Convalescence was satisfactory, and the patient was discharged from the hospital on the twelfth postoperative day. The spleen weighed 460 Gm. and measured 14.5 by 10 by 6 cm. A ragged tear measuring 4 cm. in length was present on the anterior margin. Microscopic examination showed that the red pulp was crowded with lymphoid cells of all types which tended to obscure the sinusoidal structures, but evidence of proliferation of these cells in situ was not seen. Proliferative activity of clasmatocytes on a large scale was not demonstrable. Large lymphoid cells corresponding to those described as "infectious mononucleosis cells" were fairly numerous in both the sinusoids and the pulp spaces. As far as we are aware, this is the third case of rupture of the spleen in the course of infectious mono-

217. Darley, W.; Black, W. C.; Smith, C., and Good, F. A.: Spontaneous Splenic Rupture in Infectious Mononucleosis: A Case and Pathologic Report, Am. J. M. Sc. **208**:381, 1944.

nucleosis which has been reported in the literature. A similar case was reported by King.[218]

One of the best reviews dealing with infectious mononucleosis in recent years has been written by Contratto.[219] Careful consideration has been given to a study of 196 cases of this disease in patients admitted to the Stillman Infirmary, connected with Harvard University. Reference has been made to the incidence, symptoms, physical signs, changes in the blood, heterophile test, complications, length of hospitalization, recurrences and relapses and therapy. No attempt will be made to give his conclusions in detail, but the reader who is interested in this subject is advised to give the article a careful perusal. He states that infectious mononucleosis is a benign illness, but it should be noted that elsewhere in this review there is 1 case reported of a fatality due to a spontaneously ruptured spleen. We are in accord with Contratto's statement that an accurate clinical diagnosis may be difficult on account of the variability of symptoms and other manifestations. The major problem in this disease is the making of a differential diagnosis, which can be accomplished by heterophile test and blood cell study. We are not in entire accord with his view, however, that this can always be done "easily," because it is our belief that the recognition of the atypical lymphocytes which are so characteristic of the disease requires considerable experience. He emphasizes the importance of making frequent heterophile tests and hematologic examinations for the presence of atypical lymphocytes during the course of the disease, since in infectious mononucleosis there is often a delay of days or even several weeks before the hematologic changes are conclusive enough to permit an accurate diagnosis.

Infectious mononucleosis is divided into four types by Etcheverry [220] as follows: the glandular, the pharyngeal, the febrile and the icteric. He comments that the last is less common and less known. The icteric type is divided into three groups, in one of which the diagnosis is made only by the presence of atypical leukocytes in the peripheral blood and a positive Paul-Bunnell reaction. In such cases, no other evidence of infectious mononucleosis may be present except the jaundice. He emphasizes that in some cases there may be a splenomegaly which sometimes persists for as long as five to seven years and perhaps longer. It is important to note that in a case of lymphocytic leukemia the Paul-Bunnell reaction was positive with a dilution of 1:896. The author thought that this possibly might be attributed to the repeated

218. King, R. B.: Spontaneous Rupture of the Spleen in Infectious Mononucleosis: Report of Case, New England J. Med. **224**:1058, 1941.

219. Contratto, A. W.: Infectious Mononucleosis: Study of 196 Cases, Arch. Int. Med. **73**:449 (June) 1944.

220. Etcheverry, M. A.: Mononucleosis infecciosa, Día méd. **16**:697, 1944.

injections of liver extract received by the patient. The product injected was made from sheep livers, and the possibility arises that it might contain the antigen responsible for the reaction. According to him, the Widal reaction may occasionally be positive in infectious mononucleosis.

The various clinical forms of infectious mononucleosis are discussed by Leunda.[221] According to him they may be divided into the typical and more usual types, such as glandular and anginose, and the atypical forms, which are the febrile, the rhinopharyngeal, the pulmonary and the nervous.

Comprehensive reviews of the literature bearing on infectious mononucleosis are given by Taillens [222] and by Stolinsky.[223]

Immerman [224] reports observations during an epidemic, in which he observed 200 cases of infectious mononucleosis. It is emphasized that the disease may be symptomatic or atypical and continue so for weeks or months. During this time, depression of the polymorphonuclear cells and the appearance of abnormal lymphocytes constitute the easiest clues to the diagnosis. In his experience the abnormal blood picture may continue for six months and perhaps for months longer. He calls attention to the paper by Randolph and Gibson,[225] mentioned in this review, in which they report that 24 patients with allergic conditions had typical cells of infectious mononucleosis in the blood in the percentage of 10 to 20 and negative heterophile reactions. He states that he now has 6 patients with angina pectoris with or without coronary thrombosis who also have these same cells; hence he argues that angina pectoris may cause the appearance of cells typical of infectious mononucleosis. He thus infers that the occurrence of these cells in any given pathologic condition does not necessarily indicate an etiologic relation.

It is stated by Beck [226] that Fennel, in December 1934, reported the first 4 proved cases of infectious mononucleosis to occur in Hawaii, with a case of probable infectious mononucleosis occurring in the previous

221. Leunda, J. J.: Formas clínicas de la mononucleosis infecciosa, Rev. argent.-norteam. cien. méd. **1**:381, 1943.

222. Taillens, J. P.: La maladie de Pfeiffer (angine à monocytes, mononucléose infectieuse, fièvre ganglionnaire), Schweiz. med. Wchnschr. **73**:267, 1943.

223. Stolinsky, A.: Infectious Mononucleosis: A Summary of the Literature with a Case Report, M. Rec. **157**:483, 1944.

224. Immerman, S. L.: An Epidemic of Infectious Mononucleosis, with a Report of Two Hundred Cases, M. Rec. **157**:480, 1944.

225. Randolph, T. G., and Gibson, E. B.: Blood Studies in Allergy: The Presence in Allergic Disease of Atypical Lymphocytes and Symptoms Suggesting the Recovery Phase of Infectious Mononucleosis, Am. J. M. Sc. **207**:638, 1944.

226. Beck, L. C.: Infectious Mononucleosis, Proc. Staff Meet. Clin., Honolulu **10**:53, 1944.

year in a soldier who had recently come to Hawaii. We must emphasize, however, that the disease undoubtedly was present before this time, if for no other reason than that American soldiers occupied the island of Hawaii for a good many years prior to 1934 and that it is inconceivable that the condition had not been carried to the island by persons with unrecognized disease. He points out the characteristic clinical manifestations and warns that a mild epidemic of infectious mononucleosis appeared imminent when this paper was published, in 1944. It seems likely that this might easily occur with the large number of American troops on the island.

Seven cases of infectious mononucleosis were observed during a period of four months in such widely separated places in Tanganyika Territory [227] that it would appear that the cases were sporadic and not part of an epidemic. The author deduces that since all 6 patients seen by him personally had a mild infection of the fauces the condition might be conveyed by droplet infection. While this mode of transmission is a possibility, certainly his cases afford no conclusive proof of it. He makes one interesting observation to the effect that he himself was the patient in case 2 and he first examined the patient in case 1 nine days before he began to have the symptoms of the disease. He states that in no other instance was he able to find the source of the infection or any information concerning the incubation period.

An epidemic in which 123 cases of infectious mononucleosis were observed is reported by Stevenson and Brown.[228] Hematologic changes highly suggestive of the condition were the most constant finding, as 110 of the 123 patients had a "mononuclear reaction." Some patients with infectious mononucleosis were admitted to the hospital with conditions which were thought to have had no bearing on this syndrome, such as fractures and associated Vincent infection of the mouth. One patient had a laparotomy performed for symptoms in the lower part of the abdomen which we assume were due to the characteristic abdominal pain due to infectious mononucleosis. This patient had demonstrable antibodies in her blood in a dilution of 1 : 224 the day after her admission to the hospital, and there was no appreciable alteration in the titer in the following few weeks. Glandular involvement was present in a great majority of cases. The authors had the clinical impression that the infection manifests itself differently in different hosts and may lead to erroneous diagnosis. The appearance of an apparently seronegative form of the disease occurred more frequently than was anticipated. In their opinion infectivity was not established in this limited study.

227. Reed, H.: An Outbreak of Infective Mononucleosis in Tanganyika, J. Trop. Med. **47**:42, 1944.

228. Stevenson, E. M. K., and Brown, T. G.: Infectious Mononucleosis: Preliminary Investigation of Series of Cases, Glasgow M. J. **140**:139, 1943.

Two cases of infectious mononucleosis in Negro children are reported by Johnson.[229] The author states that as far as he knows these are the first serologically proved cases of its occurrence in Negroes in the literature. He refers to a previous case in a Negro man which was reported by Longcope.[230] Johnson states that no explanation can be offered for the apparent rarity of this disease on a racial basis. Three cases of infectious mononucleosis in Negroes are reported by Ray and Cecil.[231] These comprise 12 per cent of the cases of this disease observed in the Medical College of Virginia Hospital over a period of five years. The prompt improvement which was noted in 1 patient following the administration of sulfadiazine they attribute to the control of secondary invaders. It is of interest to note that in 1 case the disease was complicated by the presence of sickle cell anemia.

It is emphasized by Mitchell and Zetzel[232] that infectious mononucleosis is a protean disease second only to syphilis in its ability to mimic other conditions. They state that in the army hospital with which they were associated the diagnosis of infectious mononucleosis was made only twice in the years 1941 and 1942. It should be noted, however, that during the year 1943, when the medical personnel became interested in the complexity of the manifestations of infectious mononucleosis, the diagnosis was confirmed in 23 additional cases. This experience is in accord with our opinion that the diagnosis of infectious mononucleosis is much more frequently overlooked than it is made. It is interesting to note that the disease was recognized in only 8 of the 34 patients at the time of admission to the hospital. The incorrect preliminary diagnoses most commonly made were nasopharyngitis, cervical adenitis, catarrhal jaundice and sinusitis. The authors emphasize correctly the fact that patients with this disease have a prolonged convalescence with persistent headache and asthenia and in some instances the diagnosis of psychoneurosis may be made unjustly. They advise that the use of the convalescent and reconditioning section of the Army Medical Corps may shorten the patient's stay in the hospital and hasten his return to active duty.

The importance of the differentiation between infectious mononucleosis and brucellosis has been emphasized by Rubenstein and Shaw.[233]

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229. Johnson, R. D.: Infectious Mononucleosis in the Negro: Report of Two Cases in Children, J. A. M. A. **124**:1254 (April 29) 1944.

230. Longcope, W. T.: Infectious Mononucleosis, Am. J. M. Sc. **164**:781, 1922.

231. Ray, E. S., and Cecil, R. C.: Infectious Mononucleosis in Negro: Report of Three Cases, with One Complicated by Sickle Cell Anemia, South. M. J. **37**:543, 1944.

232. Mitchell, R. H., and Zetzel, L.: Infectious Mononucleosis in Army, War Med. **5**:356 (June) 1944.

Among a number of possibilities, one should keep in mind both of these diseases when fever of undetermined origin is the outstanding feature of the clinical course. This problem was approached by examining for the presence of sheep cell agglutinins characteristic of infectious mononucleosis all blood specimens sent in for agglutination tests for brucellosis to the Laboratory of the Division of Communicable Diseases, Massachusetts Department of Public Health. Both tests were performed on a series of 1,000 consecutive specimens of blood serum submitted to the laboratory. In each serum in which a positive sheep cell agglutination was elicited, the physician was interviewed to obtain additional clinical and laboratory data. When the titer was less than 1:128, a second specimen was requested to ascertain the titer later in the course of the disease. They found 13 positive agglutinations of sheep cells in 1,000 specimens for testing. In only 2 of these 13 cases had the diagnosis of infectious mononucleosis been suspected. It should be pointed out, however, that in many of the patients there had been symptoms of long duration. Since infectious mononucleosis is usually an acute, comparatively brief febrile illness, it is scarcely to be expected that positive heterophile reactions would be found in the patients with long-standing symptoms. If these chronic infections had been excluded, undoubtedly the percentage of cases of infectious mononucleosis would have been appreciably greater. This study serves to remind one that in all patients with acute febrile diseases of obscure origin, the possibility that either brucellosis or infectious mononucleosis might be present should be given serious attention.

The important fact is pointed out by Lloyd [234] that purpuric phenomena, even with decided reduction of platelets, may occur in a patient with infectious mononucleosis. Purpura does not necessarily constitute an absolutely infallible diagnostic point in favor of leukemia. His patient was a youth aged 20, who had the symptoms of an infection of the upper respiratory tract and, in addition, had a characteristic lymphocytosis, with numerous large lymphocytes and atypical mononuclear forms, combined with a heterophile agglutination of 1:512. These findings were thought to be sufficient to make a positive diagnosis of infectious mononucleosis despite the absence of significant lymphadenopathy and a palpable spleen. Platelets numbered as low as 66,000 per cubic millimeter. There was no significant anemia, and the highest white blood cell count was 20,300 per cubic millimeter. Judging from this case, it is pointed out by Lloyd that severe infectious mononucleosis may be indistinguishable in its early stages from acute lymphatic leukemia, even though the

233. Rubenstein, A. D., and Shaw, C. I.: Infectious Mononucleosis Simulating Brucellosis, New England J. Med. **231**:111, 1944.

234. Lloyd, P. C.: Acute Thrombocytopenic Purpura in Infectious Mononucleosis: Report of Case, Am. J. M. Sc. **207**:620, 1944.

presence of purpura has long been considered an important diagnostic point in favor of the latter. In the light of the case at hand, however, he emphasizes that purpuric and hemorrhagic phenomena with or without thrombopenia cannot constitute a valid distinguishing feature between the two conditions. He does emphasize, however, that the finding of a well defined anemia is exceedingly rare in infectious mononucleosis and that if the condition is associated without obvious explanation one may well suspect the presence of a leukemic process. We wish to state two points in regard to Lloyd's case: (1) that purpura, although it may occur, is exceedingly rare in patients with infectious mononucleosis and is a valuable diagnostic point in differentiating acute leukemia from it and (2) that the possibility that purpura in a patient with infectious mononucleosis may be due to one of the sulfonamide drugs should always be investigated.

In an excellent review, Kaufman [235] states that he regards the heterophile antibody reaction as a laboratory procedure of considerable value in clinical medicine. He points out that one frequently speaks alternately of the Paul-Bunnell test and the sheep cell agglutination test and that in Europe the procedure is referred to as the Hanganatziu-Deicher reaction. He favors the Thompson modification of the Davidsohn method, an account of which is soon to be published. It is accurate and simple and can be interpreted in one hour. In a study of 83 proved cases of infectious mononucleosis, he concludes that there are three aspects of the disease to be considered from the standpoint of diagnosis: the clinical, the hematologic and the serologic. If any two of them give positive evidence of the disease the diagnosis may be considered established. No cases in which there was a normal blood picture were observed to show positive clinical and serologic evidence of the disease. There were many cases, however, in which there was positive clinical and hematologic evidence of the disease but normal serologic reactions and a few cases in which there was positive hematologic and serologic evidence but a subclinical or an atypical clinical picture. It is concluded by Kaufman that when sheep cell agglutination occurs in a dilution of 1:32 with the Paul-Bunnell technic and in a dilution of 1:56 with the Davidsohn technic, it must be considered indicative of the disease. An agglutination in a dilution of 1:16 with the Paul-Bunnell technic and in a dilution of 1:28 with the Davidsohn technic requires further investigation. He believes that even repeatedly negative reactions do not by any means eliminate the diagnosis of infectious mononucleosis. Kaufman found that the reaction usually becomes positive between the sixth and twenty-sixth days of the illness and most commonly

235. Kaufman, R. E.: Heterophile Antibody Reaction in Infectious Mononucleosis, Ann. Int. Med. **21**:230, 1944.

between the twelfth and twenty-first days. It usually remains positive for two to four months after the onset, although this period varies greatly and it may return to negative much sooner or not until much later. Usually reactions which are positive in high titer will be found to persist longer periods of time. He cautions that a negative reaction does not rule out the diagnosis and that a positive one does not definitely establish it. In suspected cases the test should be repeated at intervals, and if the titer rises or if the reaction becomes positive after having been negative the diagnosis is established beyond doubt, provided the patient has not received an injection of horse serum a short time before. He has also found that an increased heterophile antibody reaction may occasionally follow the administration of serum or liver extract and may occur in cases in which the final diagnosis is something other than infectious mononucleosis, as, for example, in 1 case of Hodgkin's disease and in a case of rubella. He has no explanation of these false positive reactions.

It is stated by Randolph and Gibson [225] that in performing differential white blood cell counts for patients with allergic disease they frequently noted large mononuclear cells indistinguishable from the atypical lymphocytes seen in infectious mononucleosis. The question is immediately raised whether the patients in this series might not be convalescing from infectious mononucleosis. In only 1 case, however, was the heterophile antibody reaction positive. Seven of the patients in the remaining cases had been suspected of having had infectious mononucleosis in the past, but their heterophile antibody examinations had been consistently negative. It is pointed out that in the 24 allergic patients studied the symptoms of weakness, fatigue and lassitude, commonly observed also as sequelae to acute infectious mononucleosis, frequently characterized the allergic reaction. The fact that both conditions occur frequently in young adults otherwise in good health adds to the difficulty of the differential diagnosis. To us, however, it is not clearly established that the patients with an allergic condition are more likely to have such abnormal cells in the blood as a specific change resulting from their allergic states.

The importance of jaundice as a complication of infectious mononucleosis is emphasized by Spring.[236] He cites the work of de Vries,[237] who classifies the types of jaundice occurring in the course of this disease as follows: (1) jaundice as the first symptom, followed by glandular enlargement; (2) jaundice occurring along with glandular enlargement, and (3) jaundice, with or without fever, occurring as the only symptom.

236. Spring, M.: Jaundice in Infectious Mononucleosis, Bull. U. S. Army M. Dept., 1944, no. 81, p. 102.

237. deVries, S. I.: The Icteric Form of Glandular Fever, Acta med. Scandinav. **95**:552, 1938.

In cases of the last type the blood picture and heterophile antibody reaction justify the diagnosis of glandular fever. Five cases are presented and discussed in detail, illustrating each of the three types as given by deVries. Prodromal symptoms preceding the onset of jaundice are characterized by those of acute hepatitis, namely, anorexia, nausea and at times vomiting and pain or distress in the epigastric region or in the right upper quadrant of the abdomen or in both. To the fully developed clinical picture are added jaundice, enlargement of the liver, hyperbilirubinemia, urobilinuria, biluria and impaired hepatic function. Laboratory studies show an icterus index which may rise as high as 50 units, with a serum bilirubin of 8 mg. per hundred cubic centimeters. The van den Bergh reaction is reported as being direct, delayed, indirect or biphasic. The hepatitis may last from two to twenty-two days. In 50 to 80 per cent of the cases the heterophile antibody reaction is positive. Spring feels that the hepatitis is definitely a part of the picture of infectious mononucleosis. The etiologic agent or its toxin probably attacks some portion of the liver itself. He accepts this view as opposed to the other explanation which has been offered, namely, that of enlargement of the lymph nodes about the hilus of the liver causing obstructive jaundice.

The case of a 19 year old youth who had an unusually severe case of infectious mononucleosis simulating atypical typhoid fever is reported by Boger.[238] The height of the temperature was 105.2 F., which is unusual for a patient with infectious mononucleosis. Likewise, the patient's amnesia for a week is not commonly encountered in this disease. It is of interest to note that the patient had a pertussis-like cough, which was so severe that it produced blood-streaked sputum and hoarseness, which persisted for more than two months. The report by Ziegler[216] mentioned in this review, in which he gives the findings in a fatal case of infectious mononucleosis, provides a basis for the pulmonary symptoms. Special attention in this report is devoted to the presence of jaundice in patients with infectious mononucleosis. Twenty-seven cases of jaundice are cited from the literature. It is the author's opinion that, although the jaundice has been explained on the basis of glandular obstruction, it would seem that obstruction of the biliary canaliculi due to intrinsic hepatic damage is more likely to account for this symptom. At present, however, the matter must be considered as unsettled.

The case of a 22 year old sailor is reported by Monat,[239] in which there were chills, fever, sore throat, nasal congestion and general

238. Boger, W. P.: Infectious Mononucleosis of Unusual Severity, with Review of Jaundice Cases Occurring in This Disease, South. M. J. **37**:546, 1944.

239. Monat, H. A.: Infectious Mononucleosis Simulating Acute Infectious Jaundice, Rev. Gastroenterol. **11**:114, 1944.

malaise. Four days later tenderness in the right upper quadrant of the abdomen and a moderate general adenopathy developed. There was definite jaundice of the scleras, with an icterus index which reached a maximum of about 82. The patient was febrile, with the peak temperature reaching 104 F. The typical evidences of infectious mononucleosis were present in the blood, with a sheep cell agglutination in a titer of 1:224 by Davidsohn's technic. The case is reported to point out the importance of infectious mononucleosis as a basis for icterus in a young person. The icterus "probably was due to compression of the common duct by a cluster of enlarged lymph glands," according to Monat. He thought that the absence of hepatic damage was shown by a negative result of a Hanger test, the normal duodenal drainage sequence, the fact that no organisms were grown on culture of the bile and the rapid clearing of icterus.

Two cases of infectious mononucleosis in which jaundice was present are reported by Morris, Robbins and Richter.[240] It is pointed out that in the absence of hemolysis and with an increased level of urobilinogen associated with a strongly positive cephalin flocculation reaction the presence of hepatic damage is strongly suggestive. The view is favored that when jaundice occurs in infectious mononucleosis it is not the result of pressure of enlarged glands in the liver but is dependent on actual parenchymal hepatic damage. It is also pointed out that infectious mononucleosis with hepatitis is a definite clinical picture and may occur without the presence of adenopathy and may require considerable laboratory study for its interpretation.

LYMPHOMATOID DISEASES, LEUKEMIA AND RELATED DISORDERS

General Observations.—Attempts to clarify the confusion of thought regarding the group of diseases classed as lymphomas continue to occupy the attention of authors. The inherent disadvantage under which all such attempts at classification labor is the necessity of basing them on morphologic changes which do not reflect differences in causation, clinical progress or response to therapy. Gonski and Holman[241] propose the following classification:

A. Lymphomas arising from lymphocytes and their precursors
   1. Lymphoblastic tumors
   2. Lymphocytic tumors
   3. Follicular tumors

240. Morris, M. H.; Robbins, A., and Richter, E.: Acute Infectious Mononucleosis with Hepatitis: Presentation of Two Cases, New York State J. Med. **44**:1579, 1944.

241. Gonski, A., and Holman, S.: The Lymphomata: A Suggested New Classification and General Clinical Features, Leech **14**:17, 1944.

B. Lymphomas arising from reticular cells
   1. Diffuse
      a. Hodgkin's disease
      b. Monocytic leukemia
      c. Aleukemic reticuloendotheliosis
      d. Letterer-Siwe's disease
      e. Boeck's sarcoid (probably)
   2. Localized
      a. Malignant monoblastoma
      b. One variety of reticulum cell sarcoma

C. Lymphomas arising from littoral cells (local histiocytes)
   1. Diffuse
      a. Clasmatocytic leukemia
      b. Stengel-Wolbach sclerosis, or diffuse littoral cell overgrowth
   2. Localized (a variety of littoral cell [histiocyte] sarcomas, or large-celled lymphosarcomas)

The surgical excision of malignant lymphomas is discussed by Gall,[242] who reports a series of 48 cases representing all types of such tumors in which there was sufficient localization to permit radical surgical removal of the affected lymph tissue. The average duration of life after operation was 5.2 years, and the average total duration after the onset of symptoms was 6.9 years. The prognosis for the surgically treated patients compared favorably with that for patients whose treatment was limited to irradiation. Twenty of the patients were without residual evidences of lymphoma. The author believes that radical surgical intervention has a definite place in the treatment of certain patients with malignant lymphoma.

Hodgkin's Disease.—Three histologically and clinically distinct types of Hodgkin's disease are recognized by Jackson and Parker.[243] The presence of Sternberg-Reed cells is necessary for diagnosis in all types. Hodgkin's paragranuloma, the most benign form of the disease, is characterized by relatively few Sternberg-Reed cells with many lymphocytes and without necrosis or fibrosis or evidence of invasion of the capsule of the gland. This form is essentially a disease of lymph nodes. It is compatible with a practically normal life for many years and has all the indications of being an infectious process. It may or may not become transformed into the more malignant type, Hodgkin's granuloma.

242. Gall, E. A.: The Surgical Treatment of Malignant Lymphoma, Ann. Surg. **118**:1064, 1943.

243. Jackson, H., Jr., and Parker, F., Jr.: Hodgkin's Disease: General Considerations, New England J. Med. **230**:1, 1944; Hodgkin's Disease: Pathology, ibid. **231**:35, 1944. Jackson, H., Jr.: Hodgkin's Disease, Bull. New England M. Center **6**:216, 1944.

The histologic pattern of the granulomatous forms includes many Sternberg-Reed cells, which the authors believe arise from the reticulum, conspicuous pleomorphism, infiltration of eosinophils, necrosis and fibrosis. Hodgkin's granuloma may involve any organ or tissue, except the central nervous system proper. The spleen, liver and gastrointestinal tract are frequently affected. It is the classic type of the disease and is considered by some as a neoplasm and by others as an infection. Jackson and Parker consider that the histopathologic features, clinical course and type of fever are all indicative of the infectious nature of the process. The third and most malignant form of the disease, Hodgkin's sarcoma, has all the features of a true neoplasm with highly invasive properties. It tends to occur in an older age group than do the two less malignant forms of the disease, and it may involve any organs, including the central nervous system. Hodgkin's sarcoma is distinguished from reticulum cell sarcoma by the presence of Sternberg-Reed cells. The predominant cells are probably extremely anaplastic, relatively small forms of Sternberg-Reed cells, with frequent mitoses. Transition forms of the three types of Hodgkin's disease may occur, and a more benign type may and frequently does progress to a more malignant one, but regression to a state of lessened malignancy never takes place. The authors discuss theories of etiology of Hodgkin's disease and consider that neither tuberculosis nor brucellosis have any etiologic relation to the condition. Their data indicate that Hodgkin's disease is the cause of 0.25 per cent of deaths in a general hospital.

In the University Medical Clinic, Basel, Switzerland, 126 cases of lymphogranuloma were observed in the years 1920 to 1942 inclusive, according to Lüdin.[244] Among these, 65 of the patients were females and 61 were males. The total number of patients seen during these years was 55,738, giving an incidence of lymphogranuloma of 0.226 per cent. The greatest number of patients with lymphogranuloma, 45 per cent of the total, were in the third decade of life, and this age preponderance applied both to men and to women. There were two instances of familial occurrence of the disease, in one a brother and sister and in another a mother and daughter were affected. In 3 cases the lymphogranuloma was complicated by pregnancy, and in 2 the pregnancy appeared to cause aggravation of the process. The 3 children resulting from these pregnancies were healthy when observed at the ages of 15, 8 and 4 years, respectively. One of the mothers died of lymphogranuloma nine years after her pregnancy; 1 died three

244. Lüdin, M.: Ueber Lymphogranulomatose; Diagnose und Therapie, Strählentherapie **74**:367, 1944.

years later, and the third was living four years after delivery. The author emphasizes that all patients with enlargement of the peripheral lymph nodes should have a roentgen examination of the chest, even though biopsy of a lymph node fails to establish a diagnosis. He cites such an instance in which enlargement of the mediastinal lymph nodes was found and the condition was later proved to be lymphogranuloma. In 2 of the patients reported on primary localization of the disease appeared to be in the tonsil. Lüdin discusses the symptoms, physical signs and blood values in lymphogranuloma. Leukocyte counts greater than 10,000 per cubic millimeter were observed in 67 per cent of the patients, the increase being due to neutrophils. There was a shift to more immature neutrophils in 38.2 per cent. Eosinophilia, amounting to more than 5 per cent of the circulating leukocytes, was found in only 3.4 per cent. Lymphocytopenia occurred in 94.3 per cent, monocytosis in 26.1 per cent, hypochromic anemia in 27.2 per cent and acceleration of the sedimentation rate in 97.8 per cent. For the clinical diagnosis of lymphogranuloma the author considers that the most important criteria are enlargement of the lymph nodes, intermittent fever, neutrophilic leukocytosis, lymphocytopenia and rapid sedimentation rate. Cases with involvement of bone are described, and irradiation therapy of the disease is discussed.

The case histories of 244 patients for whom the diagnosis of Hodgkin's disease was made at the Edward Hines Hospital, Washington, D. C., from 1930 to 1940 inclusive, were reviewed by Bersack.[245] Of these, 19 were excluded because of lack of biopsy, inadequate data or erroneous diagnosis. The patients in the remaining 225 cases were studied with particular reference to the determination of prognosis on the basis of the nature of the histologic changes. Necropsies were performed on 67 of the patients. The author concludes that favorable elements in the histologic picture of Hodgkin's disease comprise preservation of the follicles, absence of capsular invasion, fibrosis, trabeculation or tendency to giant follicle formation, vascularity, presence of fibroblast-like cells and persistence in abundance of the small lymphocytic elements of the node. The extent of tissue involvement bore a direct relation to the rapidity of the course of the disease. Involvement of the inguinal nodes appeared to have the same prognostic significance as generalized dissemination of the process. The lymphoreticuloma type with sarcomatous features was the most frequently occurring form of Hodgkin's disease after the age of 40 years and carried a relatively poor prognosis.

245. Bersack, S. R.: Hodgkin's Disease—Incidence and Prognosis: Statistical Correlation with Clinicopathologic Picture, Arch. Int. Med. **73**:232 (March) 1944.

Among 3,450 hospital patients there were 18 with Hodgkin's disease and 18 with pseudoleukemia (lymphadenoma?), according to Floros.[246] A history of tuberculosis was obtained from 2 of the patients with Hodgkin's disease. Irradiation was the most effective form of therapy employed. Other measures included arsenical, iron and liver preparations. Fifty-two cases of Hodgkin's disease are reviewed by Oakey.[247] There were no demonstrable predisposing or etiologic factors. Males comprised 69.2 per cent of the patients. The highest percentage of cases occurred in the age range of 50 to 60 years. The cervical region was involved primarily in 59.6 per cent, with unilateral involvement more common than bilateral. The average duration of life of 33 of the patients, presumably from the time of their initial observation, was 20.3 months. Two patients were alive five years after the first examination.

Involvement of the bone marrow in Hodgkin's disease is discussed by Steiner,[248] who reviews the literature on the subject and reports an analysis of 14 cases, in 11 of which microscopic examination of small samples of marrow revealed the changes of Hodgkin's disease. The bones were selected at random, and in thirty-eight of sixty-two sections studied evidence of Hodgkin's disease was found. The author believes that in practically every case of Hodgkin's disease lesions of the marrow would be found if enough bones could be thoroughly examined. The pain occurring in Hodgkin's disease, he thinks, may be attributed to osseous involvement. Because of the sparsity of lesions, however, it is not usually possible to explain the anemia on the basis of replacement of marrow. Aspiration of sternal marrow ordinarily fails to reveal evidence of Hodgkin's disease. Steiner points out that the distribution of the lesions in Hodgkin's disease follows more closely that of the reticuloendothelial system than that of the lymphatic system.

Vascular involvement by the lesions of Hodgkin's disease is reviewed by Salvador Júnior.[249] His own observations are based on the study of 19 cases. The changes in the vessels in Hodgkin's disease include: (1) early and extensive mobilization of endothelial elements in both blood and lymph capillaries, (2) infiltration of the walls of the capillaries by leukocytes and red blood cells, (3) in the larger vessels,

246. Floros, A.: Beobachtungen bei 18 Fällen von Lymphogranulomatose, Wien. klin. Wchnschr. **56**:270, 1943.

247. Oakey, R. S., Jr.: Review of Fifty-Two Cases of Hodgkin's Disease, Hahneman. Monthly **79**:139, 1944.

248. Steiner, P. E.: Hodgkin's Disease: The Incidence, Distribution, Nature and Possible Significance of the Lymphogranulomatous Lesions in the Bone Marrow: A Review with Original Data, Arch. Path. **36**:627 (Dec.) 1943.

249. Salvador Júnior, A.: As lesões vasculares no granuloma maligno, Portugal méd., 1943, no. 4, p. 151.

more often arteries than veins, a proliferative and obliterative "endovascularitis," frequently associated with thrombosis, (4) a "perivascularitis" also affecting the larger vessels and (5) in later stages invasion of the vessel wall by granulomatous tissue, occasionally resulting in thrombophlebitis or hemorrhage. In 4 cases diffuse necrosis secondary to vascular involvement was observed. In all cases sclerosis of vessels of varying degree was found. The author concludes that the vascular modifications occurring in Hodgkin's disease are a characteristic feature of the disease.

Intrathoracic involvement was proved by roentgen examination in 63 per cent of 55 cases of Hodgkin's disease reported by Wolpaw, Higley and Hauser.[250] However, their patients probably represent a selected group.

Actuated by earlier published reports by Parsons and Poston of the coexistence of Hodgkin's disease and brucellosis, Hoster, Doan and Schomacher [251] attempted without success to isolate organisms of the Brucella group from the tissues and body fluids of 35 patients with Hodgkin's disease and of 36 patients with miscellaneous diseases of the reticuloendothelial system.

The case of a woman aged 52 is reported by Anderson.[252] Necropsy revealed generalized enlargement of lymph nodes and splenomegaly. There was proliferation in the sinuses and medullas of histiocytic elements and of atypical cells classified as prohistiocytes. These were large cells of polygonal shape possessing nuclei rich in chromatin and with prominent nucleoli. The author points out that this condition had been previously separated from the group of diseases commonly classed as atypical Hodgkin's disease. Grossman [253] reports the case of a 68 year old woman with Hodgkin's disease, apparently limited to the abdominal cavity and complicated by macrocytic anemia and a megaloblastic reaction of the marrow which was refractory to liver therapy. The clinical course was rapidly progressive and was marked by high fever. Necropsy revealed atrophy of the gastric mucosa and patches of Hodgkin's granuloma with many megaloblasts in the bone marrow. The question whether the patient had pernicious anemia as well as

250. Wolpaw, S. E.; Higley, C. S., and Hauser, H.: Intrathoracic Hodgkin's Disease, Am. J. Roentgenol. **52**:374, 1944.

251. Hoster, H. A.; Doan, C. A., and Schomacher, M.: Studies in Hodgkin's Syndrome: A Search for Brucella in Hodgkin's Syndrome, Proc. Soc. Exper. Biol. & Med. **57**:86, 1944.

252. Anderson, R. G.: Histiocytic Medullary Reticulosis with Transient Skin Lesions, Brit. M. J. **1**:220, 1944.

253. Grossman, E. B.: Abdominal Hodgkin's Disease: No Superficial Lymph Node Enlargement; Macrocytic Anemia Resistant to Liver Therapy, J. Mt. Sinai Hosp. **10**:804, 1944.

Hodgkin's disease was left undecided. An unusual leukocyte picture presented by a woman of 78 with Hodgkin's disease is reported by Williams and Neubuerger.[254] The duration of the illness was about six months. Lymphadenopathy, hepatomegaly and splenomegaly were present, and the patient failed to benefit from roentgen ray therapy. The erythrocyte count was 2,240,000 per cubic millimeter, hemoglobin value 8.5 Gm. per hundred cubic centimeters and leukocyte count 140,000 per cubic millimeter, with a differential count of eosinophils 52.3 per cent, neutrophils 44.2 per cent, including a few myelocytes, and lymphocytes 3.3 per cent. The diagnosis was confirmed by necropsy.

A man aged 38 suffering with Hodgkin's disease, thrombopenic purpura and pulmonary tuberculosis was observed by Wright-Smith.[255] At necropsy generalized Hodgkin's disease involving the bone marrow was found. Tuberculosis was limited to the lungs. Simon[256] reports the case of a 56 year old man with Hodgkin's disease terminating in acute miliary tuberculosis. Ayerza and Cernich[257] observed a man of 38 with Hodgkin's disease complicated by pericarditis.

The case of a man aged 39 with Hodgkin's disease and disturbed vitamin A metabolism is reported by Glazebrook and Tomaszewski.[258] There was evidence of severe impairment of hepatic function and increased excretion of vitamin A, especially during febrile episodes. The patient had a generalized ichthyosiform atrophy of the skin, which was thought possibly to be the result of the abnormal metabolism of vitamin A. Sabetta[259] reports the case of a woman of 64 without enlargement of the liver, spleen or lymph nodes, with the exception of one epitrochlear node, which was removed and found to reveal Hodgkin's disease. There was a scattered erythematous papular eruption on the arms, shoulders, chest, hips and thighs. Levin[260] observed a Negro aged 32 with pea-sized to quarter-sized tender nodules of the skin of

254. Williams, W. S., and Neubuerger, K. T.: Hodgkin's Disease with Marked Eosinophilia, Rocky Mountain M. J. **41**:320, 1944.

255. Wright-Smith, R. J.: A Case of Hodgkin's Disease with Thrombocytopenic Purpura Complicating Chronic Pulmonary Tuberculosis, Roy. Melbourne Hosp. Clin. Rep. **14**:70, 1943.

256. Simon, S. M.: Hodgkin's Disease with Terminal Miliary Tuberculosis, M. Bull. Vet. Admin. **21**:97, 1945.

257. Ayerza, L., and Cernich, R.: Granuloma maligno primitivo del pericardio (caso princeps), Rev. Asoc. méd. argent. **57**:981, 1943.

258. Glazebrook, A. J., and Tomaszewski, W.: Ichthyosiform Atrophy of the Skin in Hodgkin's Disease: Report of a Case, with Reference to Vitamin A Metabolism, Arch. Dermat. & Syph. **50**:85 (Aug.) 1944.

259. Sabetta, A.: Hodgkin's Disease of the Skin, Arch. Dermat. & Syph. **49**:289 (April) 1944.

260. Levin, O. L.: Hodgkin's Disease of the Skin in a Negro, Arch. Dermat. & Syph. **49**:75 (Jan.) 1944.

the upper anterior surface of the thorax. Biopsy of one of these nodules as well as of a supraclavicular lymph node revealed the presence of Hodgkin's disease.

Mycosis fungoides apparently bears a relation to Hodgkin's disease which is not well understood. Grandbois [261] reports the case of a man of 69 with generalized cutaneous involvement and erythroderma considered to be due to mycosis fungoides. The leukocyte count reached the level of 48,000 per cubic millimeter, and 60 per cent of the cells were classified as atypical monocytes.

Uveitis believed to be directly associated with Hodgkin's disease is reported in a man of 26 by Kamellin.[262] Canfield [263] reports the case of a man aged 28 who twelve years earlier had a diagnosis made of Hodgkin's disease on the basis of biopsy of an enlarged axillary node. At that time he received roentgen ray therapy, and he was able shortly before coming under the author's observation to pass an army induction examination. Soon after he entered the armed forces, a proliferating granulomatous mass developed on the vocal cords. A diagnosis of Hodgkin's disease was made on the basis of examination of the tissue. The lesion rapidly progressed.

The case of a man of 60 with Hodgkin's disease of the stomach is reported by Jungmann.[264] Total gastrectomy and splenectomy were performed in the belief that the patient had a carcinoma of the stomach. The author suggests that the discrepancy between the extent of the changes in the mucous membrane and the persistence of peristalsis, as revealed by roentgen examination and gastroscopy, may be of value in differentiating carcinoma from lymphogranuloma of the stomach. Atypical Hodgkin's disease in a woman of 44 years, apparently limited to a small portion of ileum, is reported by Donati and Bragaglia.[265] Four months after resection of the affected portion of the intestine the patient was apparently well. The coexistence of metastatic epithelioma and malignant granuloma in a woman aged 67 is reported by Sammartino.[266]

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261. Grandbois, J.: Mycosis fongoïde à forme érythrodermique et à formules sanguines pseudo-leucémiques, Laval méd. **8**:695, 1943.

262. Kamellin, S.: Uveitis Associated with Hodgkin's Disease: Report of Case, Arch. Ophth. **31**:517 (June) 1944.

263. Canfield, N.: Laryngeal Obstruction Probably Due to Hodgkin's Disease, Proc. Roy. Soc. Med. **37**:673, 1944.

264. Jungmann, H.: Hodgkin's Disease of Stomach, Brit. J. Radiol. **16**:386, 1943.

265. Donati, A., and Bragaglia, R.: Linfogranuloma maligno primitivo de intestino com especiais caracteres blastomatosos de glandulas mesenteriais (contribuição ao estudo das formas atipicas de morbo de Hodgkin), Folia clin. et biol. **14**:103, 1942.

Surgical excisions of affected lymph nodes in 2 cases of Hodgkin's disease is reported by Puente Duany.[267] In both patients the disease later became generalized.

Lymphosarcoma.—During a nine year period 20 cases of lymphosarcoma of the gastrointestinal tract were observed at the New York Hospital, according to McSwain and Beal.[268] The total number of admissions in this period was 149,469. The ratio of lymphosarcoma to carcinoma is 1 : 51, or 1.9 per cent of all malignant lesions of the gastrointestinal tract. In their series, involvement of all parts of the tract except the duodenum was represented. It is advised that such tumors should be extirpated when possible and that irradiation therapy should always be employed. Rafsky, Katz and Krieger[269] report 11 cases of proved lymphosarcoma of the stomach and 1 in which this diagnosis was probable. All the patients were operated on. Their ages ranged from 18 to 80 years, and the clinical manifestations were variable. A case of lymphosarcoma of the stomach in which the tumor was not revealed by roentgen examination but was seen by means of the gastroscope is reported by Paul and Parkin.[270]

According to Winkelstein and Levy,[271] lymphosarcoma of the intestine is rare, more often affecting the small than the large bowel. Multiple lesions are not uncommon. The neoplasm may develop at any age, the average in their series being 43.7 years. The most common clinical manifestations are abdominal pain, loss of weight, pallor and the presence of an abdominal mass. The condition is always fatal, and even when both surgical and roentgen therapy are employed the duration of life after initial treatment is usually less than one year. Mena[272] reports the case of a man of 40 years who had suffered with episodes of abdominal pain and bloody diarrhea for two years, in whom acute intestinal obstruction finally developed. Necropsy revealed lymphosarcoma, with ulcerations involving portions of the ileum and jejunum. The patient also had a hydatid cyst of the liver.

266. Sammartino, R.: Epitelioma y granuloma maligno concomitantes, Arch. Soc. argent. de anat., norm. y pat. **4**:48, 1942.

267. Puente Duany, N.: Dos casos de enfermedad de Hodgkin a punto de partida localizado y en sitios poco frecuentes; posibilidades quirúrgicas de la enfermedad, Arch. cubanos cancerol. **2**:189, 1943.

268. McSwain, B., and Beal, J. M.: Lymphosarcoma of the Gastrointestinal Tract: Report of Twenty Cases, Ann. Surg. **119**:108, 1944.

269. Rafsky, H. A.; Katz, H., and Krieger, C. I.: Varied Clinical Manifestations of Lymphosarcoma of the Stomach, Gastroenterology **3**:297, 1944.

270. Paul, W. D., and Parkin, G. L.: Lymphosarcoma of the Stomach: A Gastroscopic Report, Gastroenterology **3**:214, 1944.

271. Winkelstein, A., and Levy, M. H.: Lymphosarcoma of Intestines: Fifteen Cases; Characteristic Sigmoidoscopic Picture, Gastroenterology **1**:1093, 1943.

272. Mena R., I.: Linfosarcoma del intestino, Rev. méd. de Chile **71**:800, 1943.

The case of a man aged 39 with lymphosarcoma of the cecum is reported by Harper, Waugh and Dockerty.[273] The tumor was successfully resected, and subsequently irradiation therapy was given. The authors point out that the behavior of lymphosarcoma of the intestine varies greatly with respect to symptoms, response to treatment and duration of life. They state that the occurrence of intussusception in an adult should always suggest the possibility of lymphosarcoma of the cecum.

Lymphosarcoma of the urinary bladder is very rare, according to Rathbun and Wehrbein,[274] who report a case and were able to find but 5 others described in the literature. Their patient was a 64 year old man with a history of recurrent cystitis extending over a period of ten years. Several tumors were present in the bladder wall, covered by intact mucosa. The rarity of the condition is attributed to the absence normally of lymph tissue in the bladder. As the result of prolonged infection deposition of lymph tissue, which may become sarcomatous, occurs.

Osseous involvement by lymphosarcoma is discussed by Bianchi and Muscolo,[275] who report the case of a boy of 17 years with roentgenologic and histologic evidence of invasion of the bones of the pelvic girdle. The primary lesions apparently occurred in a submaxillary node. Later the skull and one tibia and fibula became involved.

A girl aged 13 who exhibited generalized invasion of blood vessels by tumor cells of small lymphocytes is reported on by Radzinski and Uznanski.[276] There was no evidence of escape of neoplastic cells into the blood stream. Early and extensive involvement of the central nervous system occurred, associated with meningeal and cerebral symptoms.

Giant follicular lymphoblastoma involving the spleen and axillary and inguinal lymph nodes occurring in a man of 32 is reported on by Murray and Storr.[277] The patient was apparently well four years after roentgen therapy. Evans[278] points out that the histologic pattern of lymphadenitis of secondary syphilis closely resembles that of giant

273. Harper, S. B.; Waugh, J. M., and Dockerty, A. B.: Lymphosarcoma of Cecum: Report of Case, Proc. Staff Meet., Mayo Clin. **19**:182, 1944.

274. Rathbun, N. P., and Wehrbein, H. L.: Lymphosarcoma of the Urinary Bladder, J. Urol. **51**:31, 1944.

275. Bianchi, A., and Muscolo, D.: Linfosarcomatosis con lesiones óseas, Rev. ortop. y traumatol. **13**:79, 1943.

276. Radzinski, J. M., and Uznanski, M. E.: Generalized Lymphosarcomatosis with Marked Involvement of Brain, Illinois M. J. **85**:87, 1944.

277. Murray, J. F., and Storr, N. V.: Giant Follicular Lymphoblastoma: Report of a Case, Clin. Proc. **3**:244, 1944.

278. Evans, N.: Lymphadenitis of Secondary Syphilis: Its Resemblance to Giant Follicular Lymphadenopathy, Arch. Path. **37**:175 (March) 1944.

follicular lymphadenopathy. He cites 2 cases, in both of which Treponema pallidum was demonstrated in the affected nodes.

Puente Duany [279] studied the cellular elements of lymph tissue in healthy persons and in patients with various pathologic conditions. He found that more satisfactory morphologic examination could be performed with imprint preparations than with histologic sections. As material for general study of lymph tissue the tonsils are recommended.

Leukemia.—An analysis of 357 cases of leukemia observed at the Cleveland Clinic over a thirteen year period is presented by Haden.[280] Of these, 50 were classified as monocytic leukemia, 60 as acute myeloid, 90 as chronic myeloid, 54 as acute lymphoid and 101 as chronic lymphoid leukemia. The author emphasizes that toxemia and infiltration of organs are responsible for most of the clinical manifestations of leukemia. The youngest patient in the series was 3½ years old and suffered with monocytic leukemia; the oldest, 76 years of age, had chronic myelogenous leukemia. Monocytic and acute myelogenous leukemia affected all age groups about equally. Acute lymphogenous leukemia was most common in children; chronic lymphogenous leukemia occurred most frequently in persons of middle age. In one third of the cases, the leukocyte count did not exceed 10,000 per cubic millimeter. Patients with monocytic leukemia often suffered with hyperplasia of the gums and infections of the oral cavity. Acute lymphogenous leukemia was commonly accompanied with anemia, bleeding and arthritis. Acute myelogenous leukemia was characterized by a great variety of symptoms and signs. Chronic lymphogenous leukemia often pursued a relatively benign course. In patients with chronic myelogenous leukemia, toxemia, fever and anemia were conspicuous features.

A classification of neoplastic diseases affecting lymphatic, myeloid and reticuloendothelial tissues is given by Hadorn.[281] The cells of the reticuloendothelium are subdivided into those of reticulum and plasma cell types. Neoplastic disease of these tissues may be localized, generalized or leukemic.

An important monograph by Stodtmeister and Büchmann [282] deals with the pathology and disturbances of myeloid function in aplastic

279. Puente Duany, N.: Estudio comparativo de las celulas normales y patológicas del sistema linfoideo y en particular aquellas de los tumores y lesiones malignas de los ganglios linfáticos, Bol. Liga contra el cáncer **19**:45, 1944.

280. Haden, R. L.: Varying Clinical Picture of Leukemia (Edwin R. Kretschmer Memorial Lecture), Proc. Inst. Med. Chicago **15**:98, 1944. Haden, R. L.: The Leukemias, Cleveland Clin. Quart. **11**:55, 1944.

281. Hadorn, W.: Ueber Leukaemie und Leukosen, Praxis **33**:375, 1944.

282. Stodtmeister, R., and Büchmann, P.: Die funktionell-pathologischen Beziehungen zwischen aplastischer Anämie und akuten Leukämien, Ergebn. d. inn. Med. u. Kinderh. **60**:367, 1941.

anemia and acute leukemia. With reference to the pathogenesis of acute leukemia, the authors conclude that despite the extraordinary pleomorphism of the disease it is essentially a single or unified pathologic process. The apparent hyperplasia of marrow seen often in cases of aplastic anemia is explained by the authors as an inadequate or incomplete reactive process representing an effort at compensation for the panmyelophthisis. Evenually this disordered myeloid hyperplasia may lead to extramedullary hemopoiesis. The ultimate result may be either panmyelophthisis with fat replacement or malignant degeneration, constituting leukemia. This article, itself a review, with about 250 references to the literature, is too comprehensive for adequate treatment here and should be studied by all who are interested in the subject.

The neurologic complications of leukemia are discussed by Stodtmeister and Weicker,[283] who collected the data afforded by 300 cases presenting such complications reported in the literature. They conclude that involvement of the nervous system is not an unusual complication of leukemia and may be due to hemorrhage, infiltration or degeneration. Hemorrhagic manifestations are most common in the myeloblastic phase of chronic myelogenous leukemia and in acute myelogenous leukemia. Nervous manifestations due to pressure may result from the development of chloroma tumors in myeloblastic leukemia. Leukemic infiltration occurs especially often in chronic lymphatic leukemia, which is also frequently associated with herpes zoster. Degenerative changes in the nervous system occurring in leukemia are of obscure origin and cannot be correlated with any special form of the disease.

A series of cases, comprising 53 of chronic myelogenous leukemia and 13 of chronic lymphogenous leukemia, were studied by Grinschpun and Raventós.[284] In the myelogenous group, 38 of the patients were males and 15 were females. The average age of the males was 36.4 years and that of the females 32.8 years, whereas the extreme ages were 6 and 54 years. In this series there were two brothers with leukemia. Priapism was noted as a complication in 6 of the patients—a much higher incidence than that usually observed. Pruritus occurred frequently in patients with chronic lymphogenous leukemia. In a second article, dealing with treatment, the same authors[285] report their

283. Stodtmeister, R., and Weicker, H.: Leukämie und Krankheiten des Nervensystems, Med. Klin. **39**:551, 1943.

284. Grinschpun, S., and Raventós, E.: Estudios sobre leucemias crónicas: Casuística, sintomatología, complicaciones, hematología, y anatomía patologíca, Rev. méd. de Chile **71**:878, 1943.

285. Grinschpun, S., and Raventós, E.: Estudios sobre leucemias crónicas: Tratamiento de las leucemias, Rev. méd. de Chile **71**:1068, 1943.

results with local roentgen irradiation over the spleen, roentgen irradiation of the whole body and radium irradiation of the spleen in cases of chronic myelogenous leukemia. The results obtained from these several forms of therapy were approximately the same with respect to initial response to treatment and duration of remission. The authors observed that the response to irradiation therapy in cases of lymphogenous leukemia was slower than in cases of the myelogenous variety and that the duration of remissions in the former type was shorter. They advocate the use of arsenic in the form of solution of potassium arsenite (Fowler's solution) between courses of irradiation therapy in the treatment of leukemia.

The roentgen therapy of leukemia is discussed by Athle,[286] who reports temporary improvement after such treatment in 12 cases of chronic myelogenous leukemia and 1 of chronic lymphogenous leukemia. No benefit following roentgen irradiation was observed in 1 case of myelogenous leukemia and 1 of lymphosarcoma with leukemia.

Uhlmann and Goldner [287] believe that the elevated basal metabolic rate in leukemia is an expression of the high oxygen requirement of leukemic cells. This behavior is unlike that of other neoplastic diseases, in which malignant cells demonstrate a high degree of aerobic glycolysis and a relatively small degree of oxygen consumption. The authors present case records in support of their contention that the basal metabolic rate is preferable to the blood count as a laboratory guide in the roentgen treatment of leukemia. They found that as a rule the metabolic rate was elevated when an exacerbation of the disease was approaching and that the rate was decreased as soon as therapy became effective, a change that could be observed usually long before other clinical or laboratory manifestations became apparent. It was felt that by employing the basal metabolic rate as a guide it was possible to control the leukemic process by the use of relatively small amounts of roentgen radiation.

The present status of radioactive phosphorus in the treatment of the leukemias is reviewed by Webster.[288] In this excellent essay by a medical student, the published reports of the use of labeled phosphorus (P_{32}) are summarized and the conclusion is reached that this form of therapy is of value in the management of patients with chronic forms of leukemia but that it is useless or deleterious in the treatment of those with acute leukemia.

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286. Athle, L. H.: Radiation Therapy of Leukemia, M. Bull., Bombay **11**: 461, 1943.

287. Uhlmann, E. M., and Goldner, M.: Use of Basal Metabolic Rate in Management of Radiotherapy for Leukemia, Radiology **42**:165, 1944.

288. Webster, C.: The Use of Radio-Active Phosphorus in the Treatment of Leukemia, Texas Rep. Biol. & Med. **2**:83, 1944.

The radioactive isotope of phosphorus P_{32} is commonly prepared by the bombardment in the cyclotron of iron phosphide, a highly insoluble compound. From this substance it is the usual practice to prepare dibasic sodium phosphate (Na_2HPO), a procedure which is attended with some difficulty. Warren and Cowing [289] state that phosphoric acid (H_3PO_4) and magnesium ammonium phosphate ($MgNH_4PO_4$) are both more readily prepared from iron phosphide than is the dibasic sodium salt and that these compounds may be safely administered by the intravenous route when dissolved in 250 to 300 cc. of a solution containing 0.85 Gm. of sodium chloride and 5 Gm. of dextrose per hundred cubic centimeters for each therapeutic dose. The retention of labeled phosphorus was practically identical after administration of the three compounds tested.

That radioactive phosphorus exerts a potent and potentially deleterious influence on the elements of normal blood formation is demonstrated by the observations of Hempelmann and his associates,[290] who noted leukopenia, thrombopenia or anemia attributable to the medication in approximately one third of their patients who had received this material. The changes in the myeloid elements were not necessarily parallel. The conditions for which treatment with P_{32} was employed included chronic myelogenous leukemia, chronic lymphogenous leukemia and monocytic leukemia, leukosarcoma, Hodgkin's disease, reticulum cell sarcoma, polycythemia vera, multiple myeloma and mycosis fungoides. The authors state that the reduction of leukocytes or platelets may be so severe as to produce clinical manifestations and that the development of thrombopenia in patients treated for leukemia may be delayed for one or two months after the leukocyte count has decreased to approximately normal levels. The advisability of frequent blood studies during and after treatment with radioactive phosphorus is emphasized.

The results of roentgen therapy in a series of cases representing miscellaneous conditions are reported by Lessard.[291] Nine patients with chronic myelogenous leukemia, 2 with chronic lymphogenous leukemia, 1 with acute myelogenous leukemia, 11 with Hodgkin's disease and 14 with lymphosarcoma were treated. The patient with acute myelogenous leukemia died two months after the onset of symptoms and failed to benefit, even temporarily, from roentgen ray therapy.

289. Warren, S., and Cowing, R. F.: The Retention of Radioactive Phosphorus When Administered in Different Chemical Forms, Cancer Research **4**:113, 1944.

290. Hempelmann, L. A., Jr., and others: Hematologic Complications of Therapy with Radioactive Phosphorus, J. A. M. A. **124**:735 (March 11) 1944.

291. Lessard, R.: Quelques résultats obtenus par la radiothérapie dans les leucémies, dans les lymphosarcomes et dans la maladie de Hodgkin, Laval méd. **9**:103, 1944.

The average duration of life for 5 patients with chronic leukemia followed until their deaths, was 16.8 months. Three patients with Hodgkin's disease lived for an average of 27.6 months. The mean duration of life for 4 patients with lymphosarcoma was 8.3 months.

The role of sepsis as a complication of acute leukemia and agranulocytosis is discussed by Scharff,[292] who reports beneficial results from the use of sulfonamide preparations in the treatment of ulcerous lesions of the oral mucous membrane and other manifestations of sepsis occurring in patients with these blood disorders. In our opinion it is worthy of emphasis that the continued administration of one of the sulfanilamide derivatives, preferably sulfadiazine, is an effective means of preventing as well as treating the necrotizing infections which add so greatly to the distress of patients suffering with acute leukemia.

Two cases of leukemia associated with other forms of malignant invasion are reported by Morrison and his associates.[293] One patient, a man aged 62 years, was found to have adenocarcinoma of the rectum, and the blood at that time was reported as normal. Fifteen months later subleukemic myeloblastic leukemia developed. The second patient, a man of 58 years, suffered from carcinoma of the head of the pancreas and chronic lymphogenous leukemia. The authors state that only 21 cases of leukemia and associated malignant growths have been reported previously in the literature. Of these, 14 were cases of lymphogenous leukemia, 6 of myelogenous leukemia and 1 of monocytic leukemia. There was no predilection for any special site or type of neoplasm. It is our view that these figures give no true picture of the actual incidence of leukemia and associated malignant growth. Lymphogenous leukemia in elderly persons is usually relatively benign and of long duration. The development of carcinoma in such patients has been, in our experience, by no means infrequent, but the association has never appeared to be more than coincidental. Gruner[294] reports the association of chronic myelogenous leukemia and carcinoma of the vulva in a woman of 26 years.

Churg and Wachstein[295] reviewed the histologic observations in 97 cases of leukemia and found evidence of varying degrees of myelofibrosis without osteosclerosis in 6. Of the 6 patients 4 had chronic myelogenous leukemia and received roentgen therapy. The remain-

292. Scharff, O.: Zur Therapie der akuten Leukämien und der Agranulozytose, Wien. klin. Wchnschr. **57**:169, 1944.

293. Morrison, M.; Feldman, F., and Samwick, A. A.: Carcinoma and Leukemia: Report of Two Cases, with Combined Lesions; Review of Literature, Ann. Int. Med. **20**:75, 1944.

294. Gruner, W.: Leukämische Myelose unter dem Erscheinungsbild eines Vulvakarcinoms, Zentralbl. f. Gynäk. **67**:1562, 1943.

295. Churg, J., and Wachstein, M.: Osteosclerosis, Myelofibrosis and Leukemia, Am. J. M. Sc. **207**: 141, 1944.

ing 2 had subacute myelogenous leukemia and were not treated by roentgen irradiation. A case is described of osteosclerosis with a leukemoid blood picture in a woman of 60 years. The disease, diagnosed eight years before as chronic myelogenous leukemia, was interpreted as an instance of nonleukemic myelosis because of the long clinical course, the moderate elevation of the leukocyte count, with a small number of primitive cells, the constant presence of nucleated erythrocytes, chronic splenomegaly, absence of typical leukemic infiltrations and diversity of the cells in sites of myeloid metaplasia, with large numbers of megakaryocytes. The authors conclude from their observations and from a review of the literature that myelofibrosis not associated with osteosclerosis is apparently not uncommon in the leukemias and that osteosclerosis is often associated with nonleukemic myelosis but rarely if ever with true leukemia.

Two patients with leukemia in whom the disease was believed to be congenital are reported on by Cross.[296] The first, a boy born of Italian parents, was first seen at the age of 3 months. The second, a girl whose parents were Irish, was seen at the age of 1½ months. In both infants hemorrhagic manifestations had been present from birth, and for both the diagnosis of myelogenous leukemia was made at necropsy. The author states that the literature of the past twenty-five years includes reports of 20 cases of congenital leukemia, of which 16 were of myelogenous leukemia, 3 were of lymphogenous leukemia and 1 was of uncertain type.

A man 46 years old was found to have acute monocytic leukemia, and two years later acute myeloblastic leukemia developed in his sister, aged 43, who had lived in the same house, according to Meikle.[297]

Two cases of chronic lymphogenous leukemia are reported by Richardson.[298] They were considered of special interest because in one, that of a man of 68 years, the leukocyte count exceeded that of the erythrocytes, reaching a level of 1,475,000 per cubic millimeter, and in the other, that of a woman aged 67, the leukemia was without symptoms but was complicated by pneumonia. The infection responded favorably to treatment with sulfadiazine, but no effect on the leukocyte picture was observed.

An unusual case of chronic lymphogenous leukemia occurring in a woman of 58 years is described by Petit and his associates.[299] There

296. Cross, F. S.: Congenital Leucemia: Report of Two Cases, J. Pediat. **24**:191, 1944.

297. Meikle, R. W.: Two Varieties of Leukaemia in One Family, Brit. M. J. **2**:468, 1944.

298. Richardson, C. R.: Chronic Lymphatic Leukemia: Report of Two Cases, New York State J. Med. **44**:292, 1944.

299. Petit, L. J., and others: Chronic Lymphatic Leukemia, Minnesota Med. **26**:1060, 1943.

were severe macrocytic anemia, thrombopenia and moderate leukopenia. The percentage of lymphocytes was 69, and immature forms were not present. Plasma protein determinations revealed an albumin value of 4.81, globulin of 1.62 and fibrinogen of 2.78 Gm. per hundred cubic centimeters. Autoagglutinins were demonstrated in the plasma, but there was no evidence of hemolysis. Free hydrochloric acid was found in the gastric contents. Sternal aspiration failed to reveal significant abnormalities. No enlargement of lymph nodes was noted; there was hepatomegaly, but the spleen was not palpable. The duration of symptoms was about one and one-half years. No response to treatment occurred, and the patient died two weeks after coming under observation. Necropsy revealed chronic lymphogenous leukemia without cellular immaturity but with widespread leukemic infiltration and replacement.

The frequent association of cutaneous lesions with lymphogenous leukemia is well known. Cutaneous involvement in patients with this disease may represent infiltration of leukemic cells or may be various forms of nonspecific reaction. Bäfverstedt [300] reports the case of a man aged 77 with chronic lymphogenous leukemia, who had many cutaneous tumors consisting of lymphocytes. There was no reaction of the reticulum, and the papillary layer was free from leukemic infiltration. Machacek [301] describes the case of a man of 66 years with chronic lymphogenous leukemia, whose face and upper extremities were involved by a cutaneous leukemid. A good therapeutic response was obtained from the combined use of roentgen irradiation, locally and to the whole body. Robert [302] observed a man of about 70 years who suffered with generalized cutaneous involvement, including erythroderma and pruritus. The lymph nodes were only slightly enlarged, and the liver and spleen were not palpable. The blood values were normal except for a leukocyte count of 21,000 per cubic millimeter, with 83.5 per cent of the cells lymphocytes. There was an increase of lymphocytic elements in the sternal punctate, and biopsies of the skin and of a lymph node established the diagnosis of lymphogenous leukemia. Cornell [303] reports the association in a man aged 57 of lymphogenous leukemia with a generalized cutaneous eruption, which was most pronounced on the face and extremities. The skin was edematous, erythematous and thickened. There were also many papular

300. Bäfverstedt, B.: Fall von leukämischer Lymphadenosis mit Hauttumoren, Acta dermat.-venereol. **23**:591, 1943.

301. Machacek, G. F.: Chronic Lymphatic Leukemia (Cutaneous Leukemid), Arch. Dermat. & Syph. **48**:671 (Dec.) 1943.

302. Robert, P.: Lymphadenosis cutis universalis (lymphatisch-leukämische Erythrodermie), Dermatologica **86**:241, 1942.

303. Cornell, V. A.: Leukemia Cutis, Arch. Dermat. & Syph. **49**:75 (Jan.) 1944.

lesions consisting of leukemic infiltrations. Hansen [304] observed a man of 66 years with lymphogenous leukemia complicated by eczema pityroides. An unusual case is described by MacKee,[305] in which a man aged 68 had a leukocyte count of 64,000 per cubic millimeter but the differential formula was stated to be normal except for 7 per cent eosinophils. The patient had bullous cutaneous lesions, and the histologic picture presented by sections of these lesions was said to establish the diagnosis of lymphogenous leukemia. Cannon [306] reports the incidental discovery of chronic lymphogenous leukemia in a man of 34 years who was being treated for syphilis in the secondary stage. Weintrob [307] observed a red "paint splash" appearance of the cervix of a girl of 15 years in whom later manifestations developed leading to the diagnosis of acute lymphogenous leukemia. According to the author, this appearance of the cervix is similar to the "paint splash" appearance of the rectal mucosa of patients with leukemia described earlier by Felsen, and he believes that it may be an important early sign in leukemia.

The case of a woman of 62 years with chronic lymphogenous leukemia complicated by leukemic infiltration in the marrow spaces of the fenestral layer within the bony capsule of the inner ear is reported by Brunner.[308] There was no involvement of the endosteal or endochondral layers. Scott and Lissimore [309] report the case of a man aged 62 who suffered with chronic lymphogenous leukemia complicated by multiple attacks of mesenteric thrombosis culminating in intestinal obstruction. Treatment by irradiation and the administration of dicoumarin (3,3′-methylene-bis-[4-hydroxycoumarin]) was successful in preventing recurrence during a three and one-half month period of subsequent observation.

Falkenstein and Fowler [310] analyze the observations in 61 cases of acute lymphogenous leukemia occurring in children under 16 years of age. The incidence of leukemic and of subleukemic blood pictures were approximately equal. The course of the disease in patients with

304. Hansen, P.: Lymphatic Leukemia: Eczema Pityroides, Acta dermat.-venereol. **23**:364, 1942.

305. MacKee, G. M.: Lymphatic Leukemia with Bullous Lesions, Arch. Dermat. & Syph. **50**:143 (Aug.) 1944.

306. Cannon, A. B.: Primary and Secondary Syphilis: Chronic Lymphatic Leukemia, Arch. Dermat. & Syph. **49**:145 (Feb.) 1944.

307. Weintrob, M.: Paint-Splash Cervix in Leukemia, J. Internat. Coll. Surgeons **7**:98, 1944.

308. Brunner, H.: Changes of the Temporal Bone in Leukemia and Osteitis Fibrosa, Arch. Otolaryng. **39**: 1 (Jan.) 1944.

309. Scott, R. A. M., and Lissimore, N.: Mesenteric Thromboses in Lymphatic Leukaemia Treated with Dicoumarol, Lancet **2**:405, 1944.

310. Falkenstein, D., and Fowler, W. M.: Acute Lymphatic Leukemia in Childhood, Am. J. Dis. Child. **65**:445 (March) 1943.

leukemic leukocyte levels was generally more acute than that in children whose leukocyte counts were not abnormally high. It was concluded that roentgen therapy may be of value in relieving symptoms due to pressure of enlarged nodes but that it is valueless or actually harmful when employed in the absence of such symptoms.

Changes in bones revealed by roentgen examination of 7 children with leukemia are described by Soto.[311] In 6 of the patients localized rarefaction of the metaphysis of long bones was observed. One had generalized osteoporosis.

Drummond[312] observed reduction in the size of the spleen and lymph nodes of a boy 14 years old with acute lymphogenous leukemia after the subcutaneous injection of 2 minims (0.12 cc.) of T.A.B. stock vaccine (bacterial vaccine made from the typhoid bacillus and the paratyphoid A and B bacilli). However, no effect was noted on the degree of anemia, the leukocyte level or the clinical course of the disease.

The case of a man of 36 years with typical myelogenous leukemia is reported by Heinle and Weir.[313] The diagnosis of leukemia was made in January 1935. Roentgen therapy was employed, and thyroidectomy was performed. Arsenic in the form of solution of potassium arsenite was administered with favorable effect. Three courses of roentgen therapy were given over three and one-half years. Five months before the patient's death pleurisy with effusion developed, which was proved to be of tuberculous cause. During the final four weeks of the illness the leukocyte count decreased to normal and then to subnormal levels. The percentage of immature cells was reduced, but some evidences of immaturity persisted until his death. At necropsy miliary tuberculosis was found. Bone marrow obtained from many sites revealed only myeloid hyperplasia and metaplasia. There was no evidence of leukemic infiltration in other organs, including the spleen, which weighed 910 Gm.

The case of a man of 50 years with acute myeloblastic leukemia and rapidly progressive tuberculosis of the bronchial lymph nodes, liver and spleen is reported by Feuchtinger.[314] He comments on the difficulty of differentiating between leukemoid reactions and true leukemia in patients with active tuberculosis and states that the association of

311. Soto, J. A.: Alteraciones oseas en la leucemia del niño; estudio radiológico, Arch. de pediat. d. Uruguay **14**:415, 1943.

312. Drummond, J.: The Use of T. A. B. Vaccine in Acute Lymphatic Leukaemia, Clin. Proc. **3**:90, 1944.

313. Heinle, R. W., and Weir, D. R.: Morphologic Obliteration of Chronic Myeloid Leukemia by Active Tuberculosis: Report of a Case, Am. J. M. Sc. **207**:450, 1944.

314. Feuchtinger, O.: Tuberkulose, akute Leukämie und myeloische Reaktion, Klin. Wchnschr. **22**:669, 1943.

the two diseases has been reported rarely but that when it occurs progress of the tuberculosis is greatly accelerated.

Unusual remissions occurring in the course of subacute myelogenous (paramyeloblastic) leukemia are reported by Moeschlin.[315] In 1 of his cases there were three definite clinical and hematologic remissions, lasting seven, three and two months, respectively, before death occurred, sixteen months after the onset of the illness. In this case sternal puncture revealed proliferation of leukemic cells and normal leukopoietic elements without intermediate forms. During remission the marrow obtained by sternal puncture was completely normal. In a second case a patient with a similar form of leukemia experienced a partial remission of activity of the disease. In a third case there was temporary disappearance of cutaneous tumors and retinal infiltration. The blood and sternal punctate obtained during remission in this case revealed a considerable decrease but not complete disappearance of leukemic elements. The author concludes that in leukemia there may be either a gradual or an abrupt inhibition of maturation of all elements comprising the myeloid series. He has observed in the same patient isolated nests of cells with leukemic features and later generalized leukemic transformation of the hemopoietic tissue. He believes that the body possesses a defense mechanism against pathologic cell development, the nature of which is obscure. The presence of abnormal cells followed by their disappearance points to the existence of some immunization process. He suggests that arsenical therapy and multiple blood transfusions may aid in the establishment of such immunization. Moeschlin states that a critical review of the literature fails to disclose a single well authenticated case in which leukemia was actually cured.

Many factors have been suggested as possible precipitating agents in the development of leukemia, especially of the more acute forms of the disease. Weiss and Haines[316] observed a Negro soldier aged 28 years who experienced severe burns from the explosion of gasoline. He received treatment in the form of blood plasma and sulfadiazine and improved until the eighth day after his injury. On the ninth day abnormal blood values were discovered, and the subsequent course of his illness was progressively unfavorable until his death, on the thirteenth day of his illness. The maximum leukocyte count was 137,800 per cubic millimeter, of which myeloblasts constituted 9 per cent, premyelocytes 4 per cent and myelocytes 4 per cent. Seventy-six per cent of the cells of the bone marrow were myeloblasts. The authors

315. Moeschlin, S.: Subakute paramyeloblasten Leukämien mit mehrfachen längeren Remissionen, Deutsches Arch. f. klin. Med. **191**:213, 1943.

316. Weiss, D., and Haines, K. E.: Burn Trauma Precipitating Acute Leukemia or a Leukemoid Condition, Am. J. M. Sc. **208**:490, 1944.

suggest that the burns may have been responsible for the development of leukemia in this case.

A man of 52 years, whose case is reported by Gerbis,[317] received roentgen therapy for dermatitis caused by turpentine. The lesions extended over the hands, arms and neck, and treatment was given for a period of three weeks. About two weeks after its discontinuance the patient first noted weakness. Approximately two months later examination of the blood led to the diagnosis of aplastic anemia. Death occurred four months after the termination of irradiation therapy, and necropsy revealed the presence of subleukemic myelogenous leukemia. Rachner [318] reports the case of a 33 year old man who had been a vulcanizer for nineteen years. He suffered with chronic benzene intoxication, and his illness terminated in acute myelogenous leukemia. The diagnosis made at necropsy was chloroleukemia. In this case leukemia was considered an occupational disease.

An unusual case of myelogenous leukemia associated with hypertension and heart block in a woman aged 64 is reported by Blotner and Sosman.[319] On two occasions, but not on a third, roentgen irradiation over the heart caused the 2:1 heart block to disappear for several days. The authors suggest, without histologic evidence, that the block was due to leukemic infiltration of the bundle of His.

Case reports of monocytic leukemia characterized by ulcerating and necrotic lesions of the oral and nasal mucous membranes are reported by Aseltine,[320] Leocádio,[321] Boyd-Cooper,[322] Hatch,[323] Dodge, Black and Mugrage [324] and Sacks.[325] Subleukemic monocytic leukemia and aleukemic reticuloendotheliosis with cutaneous involvement are the subjects of case reports by Smith and his associates [326] and by Michelson.[327]

317. Gerbis, H.: Aleukemische Myelose nach therapeutischer Röntgenbestrahlung der Haut, Deutsche med. Wchnschr. **69**:540, 1943.

318. Rachner, H.: Chloroleukämie als Folge einer Benzolvergiftung, Deutsche med. Wchnschr. **70**:219, 1944.

319. Blotner, H., and Sosman, M. C.: X-Ray Therapy of the Heart in a Patient with Leukemia, Heart Block and Hypertension: Report of a Case, New England J. Med. **230**:793, 1944.

320. Aseltine, L. F.: Monocytic Leukemia with Oral Manifestations: Report of Case, J. Oral Surg. **2**:266, 1944.

321. Leocádio, J.: Leucemia monocitica, Brasil-med. **58**:83, 1944.

322. Boyd-Cooper, B.: Ulcerative Stomatitis in a Case of Subacute Monocytic Leukaemia, Brit. Dent. J. **76**:1, 1944.

323. Hatch, F. N.: Leukemia as a Cause of Nasal Obstruction: Report of a Case, California & West. Med. **61**:23, 1944.

324. Dodge, H. J.; Black, W. C., and Mugrage, E. R.: Acute Monocytic Leukemia: Case Report, Rocky Mountain M. J. **41**:177, 1944.

325. Sacks, I.: A Case of Acute Monocytic Leukemia, South African M. J. **18**:248, 1944.

(Footnotes continued on next page)

Failure to recognize the presence of acute leukemia in a patient receiving treatment for Vincent's infection of the mouth is illustrated by a case reported by Cahn.[328]

Rapid progress of leukemia in a soldier 19 years of age is reported by Julliard and Blancardi.[329] The duration of the illness was five days, and the symptoms were fever, diarrhea and hemorrhagic manifestations. Necropsy revealed replacement of normal myeloid elements by abnormal leukoblasts, with infiltration of the spleen and lymph nodes by leukemic cells classified as myeloblasts.

The subject of acute leukemia is reviewed by Ducach Grinberg [330] in a monograph. Eighteen cases observed by the author are discussed in detail. The literature referred to in this article is predominantly European.

Pérez Díaz and de la Huerta [331] report the case of a 59 year old woman with a history of jaundice of eight months' duration. The diagnosis of acute subleukemic hemocytoblastic leukemia was made by sternal aspiration. The enlarged liver contained nodules consisting of the same type of cells as those found in the marrow. Lopéz Fernández and Bidot Peralta [332] observed a youth of 18 with symptoms and signs suggestive of tuberculous peritonitis. The blood picture when the patient was first seen was not suggestive of leukemia, but the ascitic fluid contained leukemic cells. Later examination of the blood revealed the features of acute hemocytoblastic leukemia.

A case of eosinophilic leukemia in a Negro boy of 11 years is reported by Friedman, Wolman and Tyner.[333] Although the course of the disease was rapid, with death occurring approximately five months after the onset of symptoms, the cells in the peripheral blood were nearly all mature forms. The maximum total leukocyte count was 194,000 per cubic millimeter, and the percentage of eosinophils

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326. Smith, D. C.; Shafer, J. C.; Jones, P. E.; Crutchfield, A. J., and Booker, P.: Monocytic Leukemia Cutis, Arch. Dermat. & Syph. **50**:132 (Aug.) 1944.

327. Michelson, H. E.: Aleukemic Reticuloendotheliosis, Arch. Dermat. & Syph. **48**:683 (Dec.) 1943.

328. Cahn, L. R.: Necessity for Pre-Operative Investigation: Report of Case of Acute Myeloblastic Leukemia, Ann. Dent. **2**:108, 1943.

329. Julliard, J., and Blancardi, C.: Leucose aiguë leucopénique et syndrome hémogeno-hémophilique terminal, Presse méd. **50**:53, 1942.

330. Ducach Grinberg, G.: La leucemia de celulas primitivas, Chile, Impr. Univ. Santiago, 1939.

331. Pérez Díaz, R., and de la Huerta, R.: Sobre un caso de leucemia hemocitoblástica a forma ictero-hepática, Rev. méd. cubana **55**:589, 1944.

332. Lopéz Fernández, F., and Bidot Peralta, C.: Leucemia aguda hemocitoblástica a forma de ascites hemorrágica, Rev. méd. cubana **54**:560, 1943.

333. Friedman, M.; Wolman, I. J., and Tyner, H. H.: Eosinophil Leukemia with Report of a Case, Am. J. M. Sc. **208**:333, 1944.

ranged between 80 and 90. The authors review 12 other reported cases of eosinophilic leukemia. All occurred in males. The age of the patients, clinical manifestations and rapidity of progress of the disease were extremely variable. Norcross and others [334] report a case of plasma cell leukemia in a man of 73 years. Kopač [335] reports the case of a man aged 51 for whom a clinical diagnosis of aleukemic myelogenous leukemia had been made. Necropsy revealed proliferating megakaryocytes associated with myelocytes and erythroblasts within the spleen. Rather unjustifiably, it appears, the case is classified as one of megakaryocytic leukemia.

Instances of pregnancy in women suffering with leukemia are reported by van der Sar and Hartz,[336] Hochman [337] and Angelucci.[338] Hochman, who observed 2 cases, both of chronic myelogenous leukemia, in 1 of which pregnancy was interrupted and in the other of which the woman was allowed to go to term and delivered a normal child, concludes that pregnancy will neither shorten the life of the mother nor result in a leukemic child. With the latter statement there is general agreement, but it is the consensus of most observers that pregnancy has a distinctly unfavorable effect on the course of chronic leukemia.

Henshaw and Hawkins [339] compared the incidence of leukemia among physicians with that recorded for the general population, obtaining their data from the obituary lists published in *The Journal of the American Medical Association,* the mortality reports of the United States Bureau of the Census and an unpublished compilation of the United States Public Health Service. They found that leukemia was recognized 1.7 times more frequently among physicians than among white males in the general population. They suggest that exposure to roentgen rays may be responsible for the increased incidence of leukemia among physicians, although they admit that no direct proof exists that roentgen radiation acts to incite leukemia in human beings.

334. Norcross, J. W.; Holmes, G. W., and others: Plasma-Cell Leukemia, with Involvement of Bone Marrow, Spleen, Lymph Nodes, Esophagus, Lungs and Kidneys: Clinicopathological Exercise, New England J. Med. **229**:1011, 1943.

335. Kopač, Z.: Ueber die Bedeutung der Megakaryocytenleukämien, Virchows Arch. f. path. Anat. **310**:660, 1943.

336. van der Sar, A., and Hartz, P. H.: Leucemia y embarazo, Rev. Policlín. Caracas **12**:325, 1943.

337. Hochman, A.: Leukaemia and Pregnancy, J. Obst. & Gynaec. Brit. Emp. **51**:231, 1944.

338. Angelucci, H. M.: Myelogenous Leucemia Complicating Pregnancy, Am. J. Obst. & Gynec. **48**:125, 1944.

339. Henshaw, P. S., and Hawkins, J. W.: Incidence of Leukemia in Physicians, J. Nat. Cancer Inst. **4**:339, 1944.

Leukemia in domestic animals is the subject of contributions by Stonebraker,[340] Fortner [341] and Lee.[342]

Experimental Studies on Leukemia.—Differences, both qualitative and quantitative, were observed by Abels and his colleagues [343] in the utilization of pyruvate by normal and leukemic white blood cells. They found that normal cells apparently utilize less pyruvate and, in most instances, convert a greater proportion of that compound to lactate than do leukemic cells. This abnormal behavior of the neoplastic cells is not due simply to their apparent immaturity. No explanation of the inability of leukemic leukocytes to metabolize thiamine normally is offered, and what other substances may be formed by the pyruvate and by the leukemic cells are not known.

The effect of removal of various endocrine glands on the incidence of spontaneous leukemia in a susceptible strain of mice was investigated by McEndy, Boon and Furth.[344] When the thymus was removed, the percentage of animals in which leukemia developed decreased from 77 to 8 among females and from 61 to 11 among males. A lowering of the incidence of leukemia also followed ovariectomy or orchidectomy. Removal of the spleen when the animals were 28 to 48 days of age failed to influence the incidence of leukemia. In animals not operated on leukemia occurred more frequently among females than among males. White, Mider and Heston [345] found that when a diet low in cystine was fed to mice of a strain susceptible to leukemia, induced by painting with methylcholanthrene, the incidence of the disease was only 10 per cent, whereas in 90 per cent of animals receiving the same diet with cystine added leukemia developed. The incidence of leukemia was not affected by altering the lysine content of the diet; but addition of methionine to a low cystine diet increased the occurrence of the disease to the same extent as did the addition of cystine. The data suggested to the author that cystine played a role in the development of induced leukemia, perhaps associated not with its properties as an amino acid essential for growth but with some other undetermined property.

340. Stonebraker, K.: Lymphocytomatosis in a Young Calf, Vet. Med. **39**: 316, 1944.

341. Fortner, J.: Untersuchungen über die Rinderleukose, Ztschr. f. Infektionskr. **60**:215, 1944.

342. Lee, C. D.: Clinical Manifestations of Avian Leukosis, North Am. Vet. **24**:670, 1943.

343. Abels, J. C.; Jones, F. L.; Craver, L. F., and Rhoads, C. P.: Metabolism of Pyruvate by Normal and Leukemic White Cells, Cancer Research **4**:149, 1944.

344. McEndy, D. P.; Boon, M. C., and Furth, J.: On the Role of Thymus, Spleen, and Gonads in the Development of Leukemia in a High-Leukemia Stock of Mice, Cancer Research **4**:377, 1944.

345. White, J.; Mider, G. B., and Heston, W. E.: Effect of Amino Acids on Induction of Leukemia in Mice, J. Nat. Cancer Inst. **4**:409, 1944.

Kaplan and Kirschbaum [346] were unable to increase the incidence or hasten the time of onset of methylcholanthrene-induced leukemia by means of roentgen irradiation, employing both DBA and F strains of mice. Kirschbaum [347] studied the latter strain with respect to genetic and nongenetic factors which had a bearing on the development of leukemia.

A paradoxic effect of the administration of a carcinogenic hydrocarbon on the development of transplanted leukemia in mice is reported by Stamer [348] and by Stamer and Engelbreth-Holm.[349] They found that 9,10-dimethyl-1,2-benzanthracene when injected into mice either by intravenous or intraperitoneal routes was able to inhibit and also to cure transplanted leukemia when the substance was given in sufficiently large amounts and over a protracted period.

The growth of transplanted lymphosarcoma in rats is inhibited by the local actions of gastric mucin, according to Williams.[350] The effect was attributed to an augmentation of the local foreign body and inflammatory process to such a degree that the neoplastic cells were destroyed. In the peritoneal cavity the reaction was not sufficient to prevent effectively the growth of the transplanted tumor cells.

The susceptibility influence promoting the growth of transplantable leukemia in certain susceptible strains of mice is transmitted in the milk throughout the lactation period, according to Law.[351] By this means he was able to obtain growth of two transplantable lymphoid leukemias and one myeloid leukemia in normally refractory mice. Saline extracts prepared from homogenized liver, spleen or mammary gland were found to contain the susceptibility influence of myeloid leukemia, line C1498. This susceptibility influence possessed the following characteristics:

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346. Kaplan, H. S., and Kirschbaum, A.: Studies on Synergism of Leukemogenic Agents in Mice, Proc. Soc. Exper. Biol. & Med. **55**:262, 1944.

347. Kirschbaum, A.: Genetic and Certain Non-Genetic Factors with Reference to Leukemia in the F Strain of Mice, Proc. Soc. Exper. Biol. & Med. **55**:147, 1944.

348. Stamer, S.: Effect of a Carcinogenic Hydrocarbon on Manifest Malignant Tumors in Mice: Eradication of Transplanted Leukemia in Mice and Attempts at Inhibition of Other Manifest Malignant Tumors in Mice by Treatment with 9:10-Dimethyl-1:2-Benzanthracene, Acta path. et microbiol. Scandinav., 1943, supp. 47, p. 1.

349. Stamer, S., and Engelbreth-Holm, J.: Influence of Carcinogenic Hydrocarbon upon Transplanted Leukemia, Acta path. et microbiol. Scandinav. **20**:360, 1943.

350. Williams, W. L.: The Effects of Gastric Mucin on the Growth of Transplanted Tumor (Lymphosarcoma) Cells in Mice, Yale J. Biol. & Med. **17**: 311, 1944.

351. Law, L. W.: Characterization of Influence Affecting Growth of Transplantable Leukemias in Mice, Cancer Research **4**:257, 1944.

1. It underwent dialysis through parchment paper at —4 C.

2. It remained stable in a 50 per cent solution of glycerin for thirty days at —4 C.

3. Stability was retained after heating at 85 C. for twenty minutes.

4. It passed through a Seitz filter, with some loss.

5. It apparently was not inactivated by partial digestion.

Murphy and Sturm [352] found that adrenalectomy increased the susceptibility of rats to transplantable lymphatic leukemia. This particular leukemia was characterized by extension of the thymus, an organ which is stimulated, even in older animals, by removal of the adrenals. The authors advance the hypothesis that hormones influencing lymph tissue play a role in malignant conditions affecting this tissue. In a later communication the same authors [353] state that when adrenal cortex extracts, including desoxycorticosterone and a pituitary adrenotropic hormone, are given to a susceptible strain of rats the resistance of the animals to a transplantable lymphatic leukemia is increased.

While studying the effects of transplantable leukemia in rats, Sturm [354] observed that whole plasma obtained from normal and from leukemic animals showed little difference in prothrombin time, as determined by the method of Quick. When, however, the plasma was diluted, the prothrombin time of the leukemic rats was greatly prolonged in comparison to that of the normal animals. Extensive infiltration of the liver and spontaneous hemorrhages were characteristic of the rats with leukemia.

Engelbreth-Holm and Eltorm [355] demonstrated that leukemia cells in mice were distinctly more sensitive than normal cells to lowering of the body temperature.

Attempts by Thiersch [356] to transmit leukemia of human beings and of mice to chick embryos and to young chicks were unsuccessful.

Polycythemia.—The treatment of polycythemia by means of roentgen irradiation is discussed by Lahm.[357] He reports the results of such

352. Murphy, J. B., and Sturm, E.: Adrenals and Susceptibility to Transplanted Leukemia of Rats, Science **98**:568, 1943.

353. Murphy, J. B., and Sturm, E.: The Effect of Adrenal Cortical and Pituitary Adrenotropic Hormones on Transplanted Leukemia in Rats, Science **99**:303, 1944.

354. Sturm, E.: The Prothrombin Concentration in the Plasma of Normal and Leukemic Rats, Cancer Research **4**:35, 1944.

355. Engelbreth-Holm, J., and Eltorm, H.: Effect of Leukemia in Mice from Lowering of Body Temperature, Acta path. et microbiol. Scandinav. **20**: 346, 1943.

356. Thiersch, J. B.: Attempts to Transmit Leucaemia of Man and of Mice to Chick Embryo and to Young Chick by Amniotic and Intravenous Routes, Australian J. Exper. Biol. & M. Sc. **22**:57, 1944.

therapy for 12 patients who were under observation for ten years. Nine of his patients were men and 3 were women. No undesirable complications occurred in 10; 1 acquired myelogenous leukemia, and in another severe anemia developed which was thought to be due to an excessive irradiation effect since his blood values later became normal and he remained in comparatively good health. Lahm advocates treatment over all the bones rather than locally over the spleen but does not mention the use of "spray" irradiation of the whole body. He employs a total dose of 2,340 r given during a period of thirty-five to forty-eight days. The importance of differentiating between true and secondary polycythemia is emphasized. Von Jagić [358] describes the diagnostic features presented by the common anemias and polycythemia and discusses the forms of therapy available for these conditions. In the management of patients with polycythemia he recommends venesection and the administration of phenylhydrazine, reserving the use of roentgen irradiation over the long bones for severely ill patients.

A case of polycythemia occurring in a member of a family in which other members were believed to be similarly affected is reported by Laszlo and Geroefy.[359] The disease was apparently transmitted by the father to three of seven children. Glazebrook [360] reports the case of a woman aged 56 who presented the feature of koilonychia, or spoon nails, associated with polycythemia. Treatment by irradiation of the whole body was successful in controlling the polycythemia, and the abnormality of the nails disappeared. Marshall [361] reports the successful extraction of bilateral cataracts from a man of 74 years with polycythemia. Excellent colored illustrations of the ocular fundi as they appear in patients with polycythemia are included in this article. Stanton and Scharf [362] observed a man aged 47 with polycythemia complicated by hypertension and dementia precox.

To determine the effects of elevation of the erythrocyte count on tolerance to deprivation of oxygen, Wetzig and D'Amour [363] induced

357. Lahm, W.: Ueber die Röntgenbehandlung der Polyzythämie, Strahlentherapie **73**:306, 1943.

358. von Jagić, N.: Zur Klinik und Therapie der Anämien und Polyglobulien, Wien. klin. Wchnschr. **56**:59, 1943.

359. Laszlo, G., and Geroefy, K.: Ein hereditärer Fall von Polycythaemia rubra, Folia haemat. **67**:316, 1943.

360. Glazebrook, A. J.: Koilonychia and Polycythaemia Vera, Edinburgh M. J. **51**:65, 1944.

361. Marshall, J. C.: A Case of Polycythaemia Vera: Extraction of Both Lenses; Satisfactory Result, Brit. J. Ophth. **28**:481, 1944.

362. Stanton, J., and Scharf, L. E.: Polycythemia Vera Rubra (Erythremia), M. Bull. Vet. Admin. **20**:453, 1944.

363. Wetzig, P., and D'Amour, F. E.: Effects of Polycythemia and of Carrot Diet on Resistance to Anoxia, Am. J. Physiol. **140**:304, 1943.

polycythemia in rats and found no change in their resistance to anoxia when the erythrocyte count was increased by 24 per cent or 56 per cent.

Multiple Myeloma.—A review article dealing with the origin and function of plasma cells and containing an extensive bibliography was published in 1941 by Fleischhacker.[364] He discusses the anatomy, embryology, development and classification of reticulum cells and plasma cells of the bone marrow. Plasma cells, he believes, arise from undifferentiated reticulum or stem cells of the marrow. The relation of the plasma cells to multiple myeloma is considered, and the classic features of the disease are enumerated.

Blackman and his associates[365] report the case of a man aged 45 with multiple myeloma, on whom extensive studies of the serum proteins and urinary proteins were made. The Bence-Jones protein behaved like a globulin. Electrophoretically it moved as a beta globulin. It was present in increased amounts in the plasma and was believed responsible for ultimate renal failure through precipitation in the renal tubules. Harvier and Rangier[366] found large amounts of Bence-Jones protein in the urine of a patient with primary carcinoma of the kidney and extensive metastases to the bones. The protein was isolated and studied chemically. It did not appear to be either an albumose or a globulin. Its presence was attributed to the destruction of bone.

The diagnosis of multiple myeloma is discussed by Ley and Roca de Viñals,[367] who report a case. The most important diagnostic features are believed to be the elevation of the serum proteins and the characteristic changes in the marrow. Leypold[368] reports the case of a man of 46 years with multiple myeloma and terminal uremia. The blood level of cholesterol was decreased to 96 mg. per hundred cubic centimeters, and the author suggests that hypocholesteremia may be a characteristic feature of this disease. Heidenström and Tottie[369] describe a case of multiple myeloma in a man aged 39, in which the disease was complicated by extensive cutaneous and articular

364. Fleischhacker, H.: Ueber die Bedeutung der Reticuloendothelien und Plasmazellen des Knockenmarkes, Ergebn. d. inn. Med. u. Kinderh. **60**:508, 1941.

365. Blackman, S. S., Jr.; Barker, W. H.; Buell, M. V., and Davis, B. D.: On the Pathogenesis of Renal Failure Associated with Multiple Myeloma: Electrophoretic and Chemical Analysis of Protein in Urine and Blood Serum, J. Clin. Investigation **23**:163, 1944.

366. Harvier, P., and Rangier, M.: Caractères chimiques de l'albumine de Bence-Jones, Compt. rend. Acad. d. sc. **216**:131, 1943.

367. Ley, E., and Roca de Viñals, J.: Contribución al estudio clínico de los mielomas múltiples, Rev. clín. españ. **10**:86, 1943.

368. Leypold, F.: Zur klinischen Diagnostik des Myeloms (Plasmozytom), Deutsche med. Wchnschr. **70**:36, 1944.

369. Heidenström, N., and Tottie, M.: Haut- und Gelenkveränderungen bei multiplem Myelom, Acta dermat.-venereol. **24**:192, 1943.

involvement. Newns and Edwards [370] observed a woman of 45 years with multiple myeloma associated with renal and widespread subcutaneous metastases. Wolff and Nolan [371] report the case of a Negro woman of 44 years, believed to be the first recorded of multiple myeloma originating in the mandible. Brehant [372] reports the occurrence of a solitary plasmocytoma in the tibia of a man aged 66. Bence-Jones protein was demonstrated in the urine. The case is considered unusual because of the age of the patient. It is stated that solitary plasmocytoma is, as a rule, seen only in young adults. Gordon and Walker [373] observed a woman of 30 years with a plasmocytoma of the upper lobe of the left lung. The site of origin of the tumor was undetermined. Rubinstein [374] reports the case of a boy who began to have pain in the left hip at the age of 12 years, ultimately suffering a pathologic fracture. The diagnosis of multiple myeloma was made by sternal aspiration when he was 15 years old. Changes in the plasma proteins and the appearance of Bence-Jones protein in the urine did not occur until later. Keefer and others [375] describe the case of a man aged 56 years with plasma cell myeloma of the liver and bone marrow. The clinical diagnosis had been cirrhosis of the liver. Hernández Morales [376] reports a case of multiple myeloma in a 50 year old Puerto Rican man, in which 65 per cent of the sternal marrow cells consisted of plasmablasts and plasmacytes.

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370. Newns, G. R., and Edwards, J. L.: A Case of Plasma Cell Myelomatosis with a Large Renal Metastasis and Widespread Renal Tubular Obstruction, J. Path. & Bact. **56**:259, 1944.

371. Wolff, E., and Nolan, L. E.: Multiple Myeloma First Discovered in the Mandible, Radiology **42**:76, 1944.

372. Brehant, M.: Plasmocytome solitaire du tibia, J. de chir. **58**:98, 1941-1942.

373. Gordon, J., and Walker, G.: Plasmocytoma of the Lung, Arch. Path. **37**:222 (March) 1944.

374. Rubinstein, M. A.: Multiple Myeloma in a 15 Year Old Boy, New York State J. Med. **44**:2491, 1944.

375. Keefer, C. S.; Castleman, B., and others: Plasma-Cell Myeloma Involving Liver and Bone Marrow: Clinico-Pathological Exercises, New England J. Med. **230**:774, 1944.

376. Hernández Morales, F.: A Case of Multiple Myeloma, Bol. Asoc. méd. de Puerto Rico **36**:278, 1944.

(To Be Continued)

News and Comment

GENERAL NEWS

National Gastroenterological Association 1946 Award Contest.—The National Gastroenterological Association announces the establishment of an annual cash prize of $100 and a certificate of merit for the best unpublished contribution on gastroenterology or allied subjects. Certificates will also be awarded those physicians whose contributions are deemed worthy.

Contestants residing in the United States must be members of the American Medical Association. Those residing in foreign countries must be members of a similar organization in their own country. The award is to be made at the annual convention banquet of the National Gastroenterological Association, to be held at the Hotel Pennsylvania in New York city on Thursday evening, June 20, 1946.

All entries for the 1946 prize should be limited to five thousand words, typewritten in English, prepared in manuscript form, submitted in five copies and accompanied with an entry letter; entries must be received not later than May 1, 1946. They should be addressed to the National Gastroenterological Association, 1819 Broadway, New York 23, N. Y.

Urology Award.—The American Urological Association offers an annual award "not to exceed $500" for an essay (or essays) on the result of some specific clinical or laboratory research in urology. The amount of the prize is based on the merits of the work presented, and if the Committee on Scientific Research deems none of the offerings worthy no award will be made. Competitors shall be limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years. All interested should write the Secretary for full particulars.

The selected essay (or essays) will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Netherland Plaza Hotel, Cincinnati, Ohio, July 22-25, 1946.

Essays must be in the hands of the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis 3, Tenn., on or before July 1, 1946.

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